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EFFECTS OF AIR POLLUTION ON JAPANESE CIVILIAN POPULATION

by

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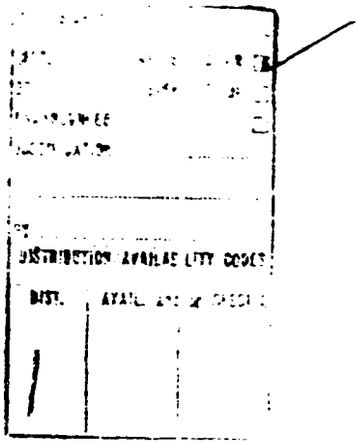
August 1968

U. S. ARMY RESEARCH AND DEVELOPMENT GROUP
FAR EAST
APO San Francisco 96343



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The Contract

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THE LIST OF PARTICIPANTS:

The present research project was conducted under the participation of the doctors, Cardiopulmonary Laboratory, Department of Medicine, School of Medicine Keio University, Tokyo, Japan.

The Principal Investigator expresses his sincere appreciation for their participation by listing their names hereunder:

Dr. Fumihiko Tamura

Dr. Koh Nakamura

Dr. Yasuyo Ohta

Dr. Makoto Mitsufuji

Dr. Tomoyuki Tomita

Dr. Takao Watanabe

Dr. Susumu Era

Dr. Hirohisa Ohtsuka

Dr. Kuniyoshi Suzuki

Dr. Takeo Kawashiro

Dr. Kenichi Goml

SUMMARY:

The studies were conducted originally aiming to investigate the effects of air pollution among Japanese civilian population. The pulmonary function studies and the clinical observation on the Japanese population in Tokyo-Yokohama area were included.

The pulmonary function studies included:
a. the assessment of the spirometry and the mechanics of breathing repeatedly done on the limited population.

b. the baseline studies on the routine pulmonary function tests.

c. some fundamental observations of the airway resistance, the AaD and of CO pulmonary diffusing capacity on the cases of normal healthy as well as of chronic pulmonary diseases.

d. effects of bronchodilator and of cigarette smoking on the ventilatory capacity and on the alveolar gas exchange.

The year-round clinical observations were performed on the population with regard to the incidence of bronchitics and the correlation of this incidence with the cigarette smoking habit.

In conclusion we were able to establish the diagnostic criteria for the pulmonary function studies to be done on Japanese population. We were also able to emphasize the physiological significance of AaD, especially of the arterial(or urinary)alveolar nitrogen tension difference, to evaluate the impaired alveolar gas exchange due to air pollution bronchitis.

On the clinical observation we observed significantly higher incidence of bronchitic patients during the winter season. We were not able to confirm the relation of this higher incidence with the cigarette smoking habit.

TABLE OF CONTENTS:

LISTS OF ILLUSTRATIONS AND TABLES:

1. PURPOSE OF THE STUDY:

Since Col. Hueber et al. described the sudden endemic incidence of the asthmatic episode among U.S. military personnel stationed in Yokohama area, Japan in 1954 the attention was focused upon these clinical symptoms of nocturnal dyspnea with wheezing as well as their pulmonary function impairment. Observation on the pulmonary physiology was continued at the U.S. Army Hospital at Zama, Kanagawa, Japan. Some epidemiological analysis was also done in parallel to the clinical- and the experimental observations. But many Japanese chest physicians did not even interested upon this kind of asthmatic patients among Japanese inhabitants living in this air-polluted Tokyo-Yokohama area. The chest physicians did not noticed or they were rather suspicious on the existence of this peculiar chest diseases.

Continuous clinical investigations were done by the U.S. Army Medical Corps on this particular diseases for years and the etiology of this peculiar symptoms was assumed to be the air pollution in this Tokyo-Yokohama area, Japan. Recently the incidence of this peculiar disease decreased year-by-year and any acceptable explanations on this decreased incidence is not yet given definitely.

In the recent few years the clinical interests on the airborne pulmonary diseases among Japanese inhabitants were stimulated and also the incidence of airborne bronchitis in this Tokyo-Yokohama area was reported to be increased.

This present study was originally planned to make intensive analysis on the clinical respiratory physiology among Japanese population in Tokyo-Yokohama area to allow one making comparison of the effects of air-pollution between the American- and the Japanese populations.

The problems we were concerned with were: 1) to conduct the baseline studies of pulmonary functions on the Japanese population, 2) to establish the most appropriate method for evaluating the pulmonary function impairment due to air pollution, 3) to make any year-round clinical observations upon the limited population of Japanese inhabitants and 4) to make it clear whether or not the patients, who reveals similar symptoms with Tokyo-Yokohama asthma seen among U.S. military personnel, are really existed in the Japanese civilian population.

The so-called diffuse obstructive pulmonary diseases may be characterized by the clinical findings as well as its spirographic changes accompanied by the depressed FEV1%. We were rather suspicious on the physiological appropriateness to take FEV1% as a parameter to detect the airway obstruction seen in cases with airborne bronchitis.

We were also interested in the low arterial 02 saturation observed by Lt.Col.Phelps(retired) on this particular patients with Tokyo-Yokohama asthma. This low arterial 02 saturation suggested us the increased venous admixture-like effects probably due to the uneven ventilation-perfusion ratio distribution. The fact suggested us making new approach to evaluate the impaired respiratory physiology in the airborne pulmonary diseases with the measurements of arterial(or urinary) alveolar nitrogen tension difference.

The present paper is consisted of three major parts, namely(1) studies to establish any sensitive,reliable methods for detecting the pulmonary function impairment due to the airborne pulmonary diseases,(2) some baseline studies on the routine pulmonary functions in Japanese civilian population, and (3) some clinical observations on the Japanese civilian population in the air-polluted area of Tokyo and Yokohama.

2. REPRODUCIBILITY OF THE SPIROGRAPHIC TESTS:

a.PURPOSE OF THE STUDY:

For the diagnostic purposes it is necessary to establish the normal limits on every parameters of the lung volumes and of the ventilatory capacity. The statistically obtained rejection limit was considered rather essential than the mathematical mean of the data on the normal healthy for the diagnostic purposes. Many investigators have already given various regression equations for the mathematical mean for the normal healthy. But very few has referred to the statistically treated data for the rejection limits of normal values. We have done some statistical analysis through the two different approaches. One of them was to make spirography repeatedly on the limited cooperative subjects and the other appraoch was done by making spirography upon the unlimited population of "healthy"subjects.

b.METHODS AND SUBJECTS:

The experiments were performed to examine the reprodu-

cibility of the routine spirography repeatedly performed on the limited subjects. The spirography was done on the cooperative volunteers on the standing position with the respirameter of 13.5L Benedict-Roth type.

As for the subjects six medical doctors, who have enough experience in the pulmonary function tests, 12 medical students and 12 cooperative patients accompanied by chronic diffuse pulmonary diseases(Table 1). Except for the doctors served as the subjects they were not informed on the purpose of the experiments.

On the doctors ten repeated spirography was performed with intervals, which were assumed sufficient to recover from the preceeding spirography, in one day and the same tests were continued on every successive six days. On every medical students ten spirography was repeated in one day and on every chest patients five spirography were made successively with sufficient intervals. Thus 600 spirograms were taken on the six doctors,120 on the twelve medical students and 60 on the twelve chest patients.

The parameters were represented by percentage for the corresponding predicted values if it is necessary. The mathematical mean were calculated to compare the spirographic parameters regardless with the difference of each individual difference in the physical constitution.

Some preliminary tests were made. The effect of various factors or conditions on the spirography was preliminarily studied. The spirography was done 30 minutes and one hour after meal as well as prior to eat. The vital capacity, FEV1% and MVV were shown in table 2 indicating the temporary decrease in vital capacity. This decrease in vital capacity seemed consistent although this decrease was only approximately 200 ml. This decrease in vital capacity was observed in every five independent observations. Either FEV1% or MVV did not changed significantly.

The vital capacity is said to decrease during sleeping and this change was explained by the probable formation of collapsed alveoli. We have measured the spirographic characteristics right after waked up and after daily activities. The subjects were requested neither to take any deep breath nor to make any thigh before the spirogram was taken early in the morning. By comparing these couples of spirographic data we found slight decrease in vital

SUBJECTS

group of subjects	spirography per person	number of subjects	total no. of spirography
MD: doctors	100	6	600
MS: medical students	10	12	120
PT: patients	5	12	60

Table 1. The subjects for the study

EFFECTS OF SLEEPING

	right after awakening	after daily activities
VC (L)	3.84	3.99
FEV_1%	95.1	94.3
MVV(L/min)	159	170

SUBJECT K.N.

Table 2. The effects of sleeping on the spirographic data

EFFECTS OF EATING

	30 min. after eating	1 hr. after eating
V C (L)	3.82	4.04
FEV_1%/%	90.4	93.3
MVV(L/min)	215	216

SUBJECT; K.N.

Table 3. The spirographic changes before and after eating.

STANDARD DEVIATION

no. of tests	doctors n = 600	students n = 120	patients n = 60
V C	2.30	2.42	6.45
FEV_1	2.29	3.04	5.42
FEV_1%	2.35	2.98	6.74
MMF	5.76	6.45	8.91
MVV	6.58	7.21	9.11

Table 4. The standard deviation of the spirographic data collected on the limited populations of subjects.

capacity right after sleeping although it was not statistically consistent. The effects of cigarette-smoking will be discussed elsewhere. Thus we asked the subjects neither to smoke cigarettes nor to eat at least 30 minutes prior to the tests. We also avoided to make tests early in the morning and asked the subjects to take deep breath prior to the spirography.

c.RESULTS:

Taking percent deviation from the mathematical mean the frequency distribution curves were drawn on vital capacity,FEV1,FEV1%,MMF and on MVV(Figures 1,2,3,4,and 5). These frequency distribution for each parameters revealed normal distribution with the standard deviation of various dimensions. The vital capacity,FEV1 and FEV1% demonstrated distribution accompanied by any smaller standard deviation while MMF and MVV had larger standard deviations. In Table 4 we have summarized the standard deviations on these five parameters obtained on these three different groups of subjects. Basing upon these data obtained on the repeated spirography the statistical analysis enabled us to calculate the 95% confidence interval for the mean on each parameters.

Ten repeated spirography was done on the 12 healthy volunteer medical students, who were sufficiently cooperative but not experienced in the tests, with sufficient intervals of five to ten minutes.

We have picked up at-randomly the three, five or ten spirograms taken on each students to calculate the 95% confidence intervals for the mean.

In the Table 5 these confidence intervals on vital capacity,FEV1,FEV1%,MMF and MVV were indicated. Numbers of tests referred to in the table designates the numbers of spirograms picked up out of a set of ten spirograms taken successively on an subject. The 95% confidence interval was significantly smaller when the numbers of spirograms were increased. When the spirography was repeated less than three timed the confidence interval came out appreciably large. As one can expect from the standard deviation already referred to. the 95% confidence intervals for vital capacity,FEV1 and FEV1% were consistently smaller than those for MMF and MVV.

The same statistical analysis was performed on

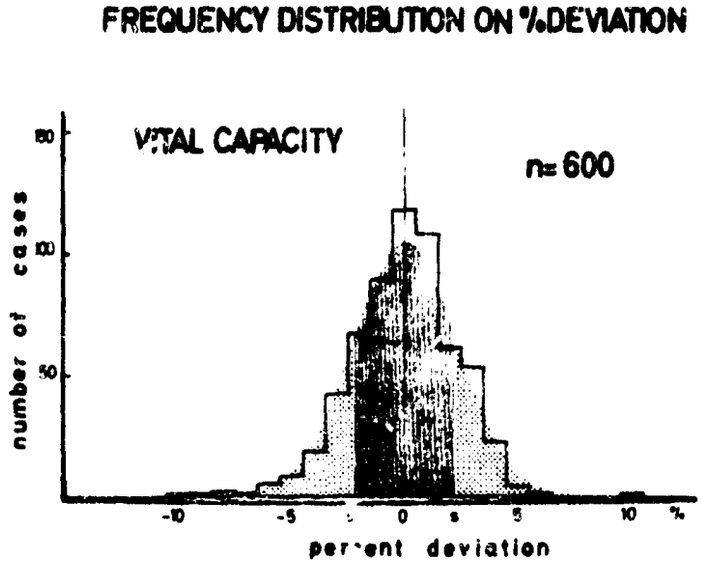

Fig.1. The frequency distribution of the vital capacity on 600 spirography.

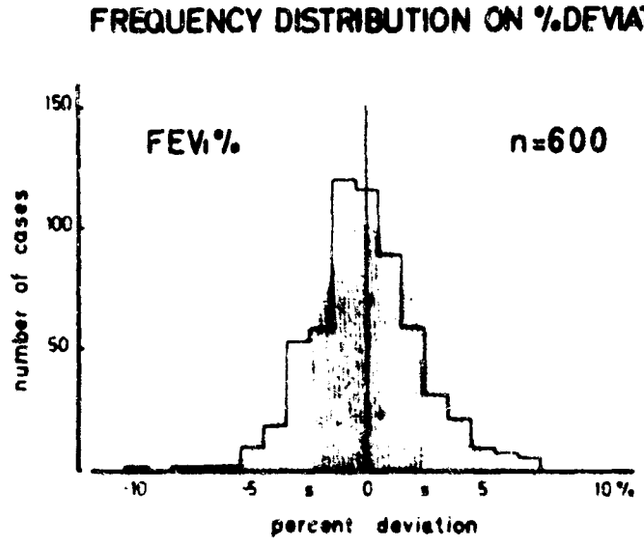

Fig.2. The frequency distribution of FEV1% on 600 spirography.

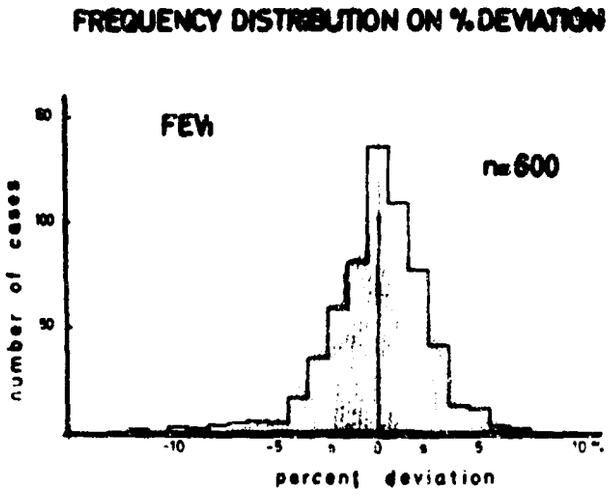

Fig.3. The frequency distribution of FEV1 on 600 spirography.

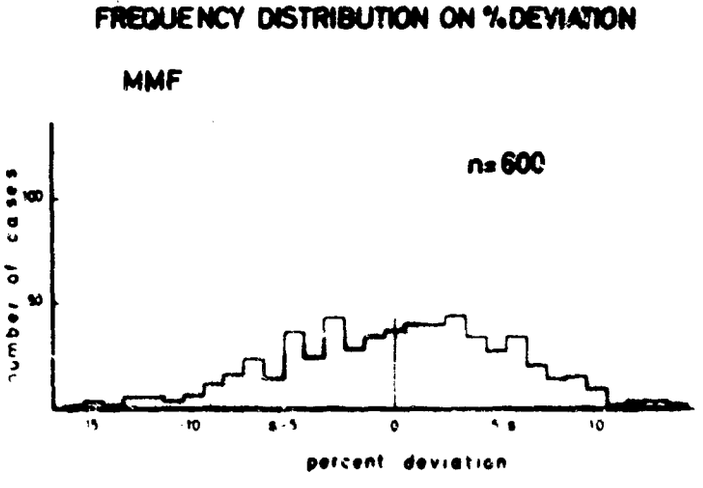

Fig.4. The frequency distribution of MMF on 600 spirography.

groups of the medical doctors and of the chest patients. Data obtained were summarized in Tables 6and 7. One can compare the 95% confidence interval calculated on the same numbers of spirograms on three different groups of independent subjects. The best reproducibility for every parameters was obtained on the group of experienced medical doctors while the most poor results were obtained on the group of chest patients(Figs.6,7,8,9 and 10). This suggested us the contribution of either the subjects' technical skill or their cooperation to be related to the results. The difference of the 95% confidence intervals for the mean obtained on the doctors with those on the chest patients was significant with regard to most of the parameters except for the vital capacity. The difference in the 95% confidence intervals for every parameters was not consistent enough between the medical doctors and the medical students.

For the convenience's sake this 95% confidence intervals ,which were previously represented by the percentage for the mean,were converted into the equivalent real figures, which may appear on the average Japanese young adult with the standard physical constitution(Tables8 and 9). In practice it would be much helpful to realize the dimensions of the reproducibility by representing the 95% confidence intervals on the real figures rather than on the percentage. Out of 600 spirograms obtained on each six doctors or out of 120 spirograms on twelve medical students three, five or ten spirograms were picked up at random to calculate the 95% confidence intervals on the corresponding groups of the spirogram. In these tables were shown the mean of these 95% confidence intervals, which of course revealed the same tendency as being found in the percent deviation on these parameters.

The 95% confidence intervals calculated on the at-randomly selected spirograms were shown. When the numbers of spirograms increased one can expect the 95% confidence intervals become smaller. The vital capacity and the FEV1 on the at-randomly selected three spirograms revealed the confidence intervals of approximately 300 ml. These confidence intervals decreased to approximately 120 ml when we took ten spirograms. On FEV1% 95% confidence intervals was found 6.3% for three spirograms, 3.2% for five spirograms and 1.5% for ten spirograms. The 95% confidence intervals for MMF and MVV revealed larger values as compared with those for other parameters.

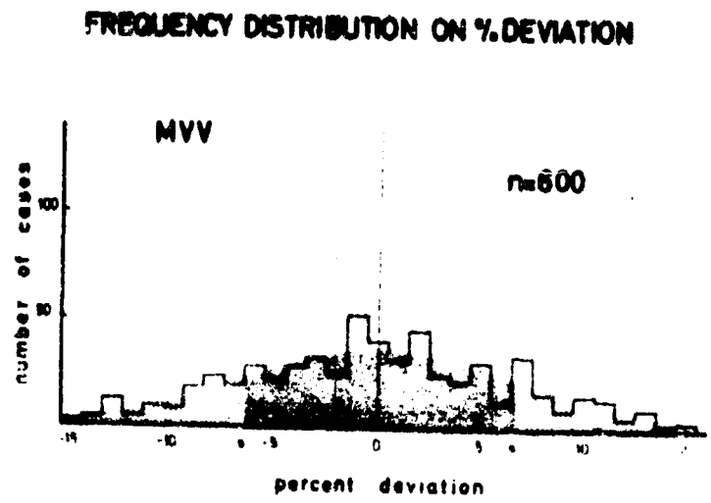

Fig.5. The frequency distribution of MVV on 600 spirography.

95% CONFIDENCE INTERVALS ON %DEVIATION

10 REPEATED TESTS ON EACH 12 STUDENTS

no. of tests	n = 3	n = 5	n = 10
V C	14.7	6.1	3.4
FEV_1	17.6	6.8	4.0
FEV_1%	15.2	7.8	3.5
M M F	31.7	15.2	9.2
M V V	31.6	18.0	10.3

Table 5. 95% confidence intervals calculated on 10 repeated tests on each 12 students.

95% CONFIDENCE INTERVALS ON %DEVIATION

RANDOM SAMPLES FROM 100 TESTS
ON EACH 6 DOCTORS

no.of tests	n=3	n=5	n=10
V C	7.5	4.4	3.3
FEV_1	7.9	4.6	2.9
$FEV_1\%$	9.2	6.0	5.0
M M F	27.2	14.2	7.6
M V V	26.7	16.6	8.6

Table 6. 95% confidence intervals calculated on 100 spirograms on each 6 doctors.

95% CONFIDENCE INTERVALS ON %DEVIATION

THE AVERAGE FOR 12 SERIES
CHEST PATIENTS

no.of tests	n=3	n=5
V C	12.7	8.6
FEV_1	22.0	11.5
$FEV_1\%$	20.8	18.8
M M F	40.1	22.6
M V V	33.0	21.6

Table 7.95% confidence intervals calculated on chest patients.

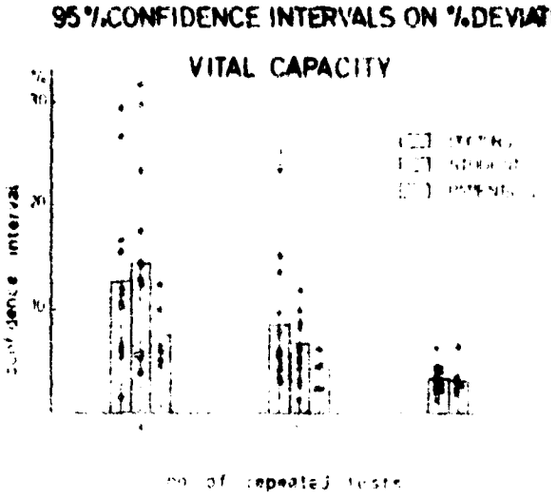

Fig.6.95% confidence intervals for vital capacity

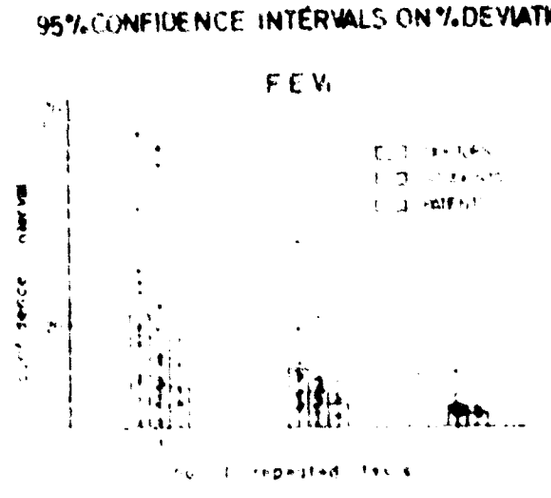

Fig.7.95% confidence intervals for FEV1.0

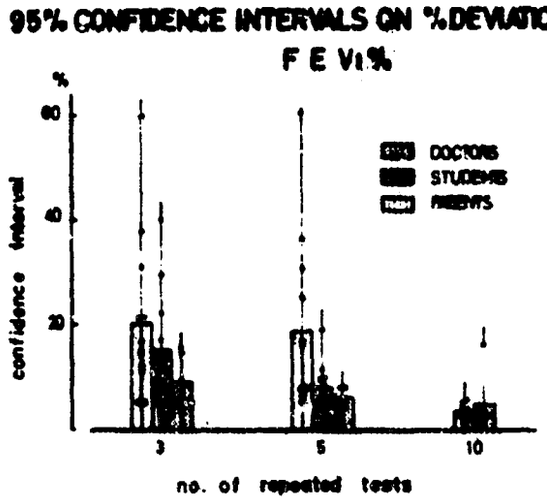

Fig.8. 95% confidence intervals for FEV1%

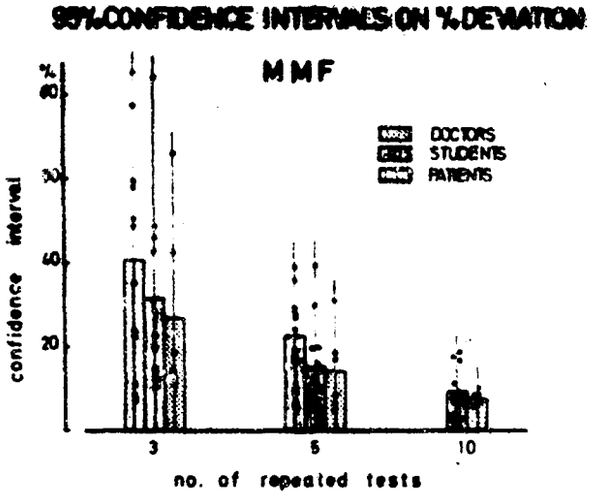

Fig.9. 95% confidence intervals for MMF

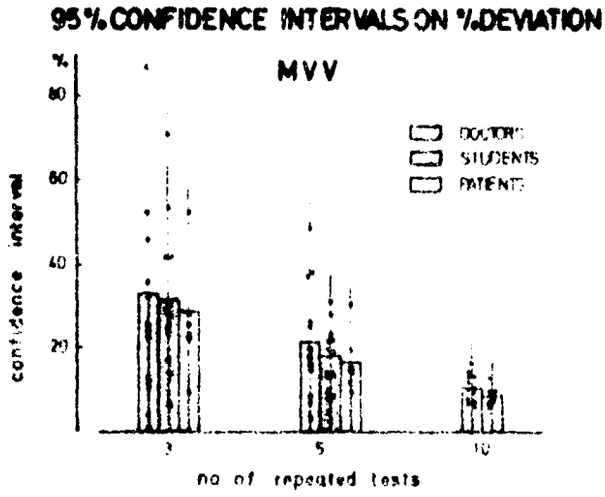

Fig.10. 95% confidence intervals for MVV

95% CONFIDENCE INTERVALS FOR THE MEAN

RANDOM SAMPLES FROM 100 TESTS
ON EACH 6 DOCTORS

no of tests	n=3	n=5	n=10
V C (L)	0.30	0.18	0.1
F.E.V_1(L/sec)	0.29	0.17	0.11
F.E.V_1 %/%	7.5	4.9	4.1
MMF(L/sec)	1.23	0.6	0.3
MVV(L/min)	31	19	10

Table 8. 95% confidence intervals for the mean calculated on six doctors.

95% CONFIDENCE INTERVALS FOR THE MEAN

10 REPEATED TESTS ON EACH 12 STUDENTS

no. of tests	n = 3	n = 5	n = 10
V C (L)	0.59	0.24	0.14
F E V_1 (L/sec)	0.65	0.25	0.15
F E V_1%	12.5	6.4	2.9
MMF (L/sec)	1.59	0.68	0.41
M V V (L/min)	37	21	12

Table 9. 95% confidence intervals for the mean calculated on 12 medical students.

95% CONFIDENCE INTERVALS ON % DEVIATION

5 TESTS IN EACH 12 SERIES
6 MEDICAL DOCTORS

no. of tests	n = 5
V C	5.6
F E V_1	4.5
F E V_1%	6.1
M M F	11.2
M V V	11.0

Table 10. 95% confidence intervals for % deviation calculated on six medical doctors.

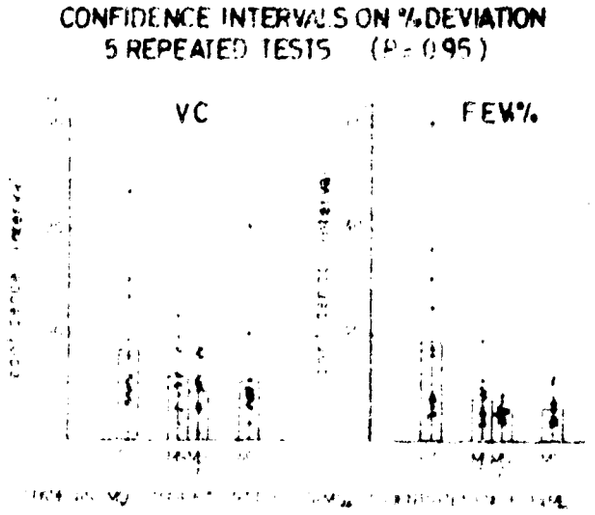

Fig.11. Confidence intervals on % deviation

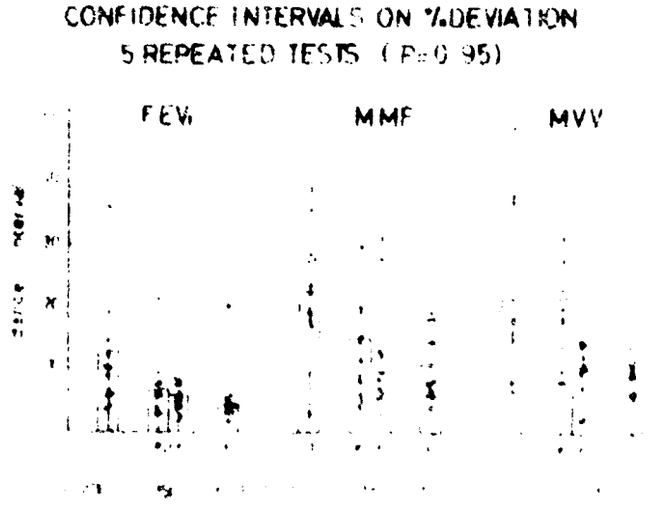

Fig.12. Confidence intervals on % deviation

d. CONCLUSIVE COMMENTS:

Through the over-mentioned experimental analysis on the repeated spirography we may be able to conclude the experiments by the following comments.

1) By some statistical analysis the reproducibility for the spirography were established.

2) The 95% confidence intervals on the %VC and on FEV1% were consistently smaller than those on MMF and on %MVV.

3) The 95% confidence intervals for the mean on the most spirographic parameters obtained on the experienced doctors were found consistently smaller than those for the cooperative medical students. The most poor reproducibility was found on the chest patients although they were cooperative enough.

4) With regard to the confidence intervals the %VC and FEV1% was found to be the best combination as for the routine diagnostic parameters on the ventilatory functions.

5) To detect any obstructive changes routinely FEV1% may be used although it is not very sensitive enough. Upon giving diagnosis by FEV1% the lower rejection limit instead of the mathematical mean for the normal healthy should be used. The 5% lower rejection limit might be lower than 70% on the aged (The detailed data will be shown elsewhere).

3. THE PULMONARY FUNCTION SURVEY ON THE UNLIMITED POPULATION OF JAPANESE CIVILIAN:

a. PURPOSE OF THE STUDY:

A baseline study on the ventilatory functions among Japanese civilian population in Tokyo-Yokohama area was done at Keio University Hospital. This series of studies were expected to give us some diagnostic criteria on their ventilatory function tests. We aimed to demonstrate the normal limits of ventilatory functions as well as to visualize the scattered distribution of the so-called normal values, which usually are referred only by the mathematical mean. We were especially concerned on the random

difference of the measured values obtained on different healthy subjects.

b.METHODS:

The routine pulmonary function tests including the lung volume study as well as the ventilatory capacity tests were done on the Japanese volunteer subjects. The spirography was done on the supine- as well as on the standing position by use of the 13.5L respirometer of Benedict-Roth type. Functional residual capacity was measured by the helium dilution method with the closed circuit system.

c.SUBJECTS:

2423 volunteers, who were on the specially organized medical checkup program during one week's hospitalization at the Keio University Hospital. Included were 1829 males and 594 females and their age ranged from 18 to 85. Out of these subjects included were 594 healthy male subjects, who revealed neither any subjective complaints nor any abnormal objective physical findings.

d.RESULTS AND TREATMENT OF THE DATA:

(1) CORRELATION WITH VARIOUS FACTORS AND THE REGRESSION EQUATIONS FOR THE MATHEMATICAL MEAN:

These so-called healthy subjects were picked up with regard to their routine clinical findings including the chest X-ray findings. As for the first step the possible factors affecting these physiological parameters were statistically examined by calculating the correlation coefficient. The sex and age were found to be the most common variables related to every parameters on the ventilatory capacity. These subjects were classified with regard to their sex and ages. Age classification was done at every five years intervals.

The parameters, which appeared to be dependent to the physical constitution, were represented as the ratio to the predicted values. This procedure was taken to eliminate the constitutional difference on each individual subjects. For the convenience's sake the predicted values were calculated by the Baldwin's formula.

age group (yr.)	no. of subjects
20 -- 29	23
30 -- 39	169
40 -- 49	476
50 -- 59	671
60 -- 69	401
70 -- 79	71
80 -- 89	18
total	1829

Table 11. Age distribution of male subjects

+ correlated
− not correlated

	%VC	FEV10%
age	±	−
obesity index	+	−
smoking habits	−	−
cough, sputum	+	−
B-R respirometer	−	−
period	−	−
no. of tests		−

Table 12. Factors influenced upon VC & FEV1.0

Table 13. Ventilatory functions of Japanese of various ages.

The data shown in this table are obtained on 468 males, who were clinically considered healthy. These healthy subjects were picked up from 2400 cases through the medical checkups at the Keio University Hospital.

age groups	no.of subjects	vital capacity (ml/cmHt)	FEV1% (%)	MVV (L/min.m^2BSA)
20-29	8	24.7(2.4)	85.5(6.2)	79.9(12.8)
30-34	18	25.1(2.4)	82.8(6.4)	75.2(16.5)
35-39	44	24.4(3.2)	83.0(6.8)	70.6(12.4)
40-44	45	24.5(3.4)	80.8(6.9)	71.4(12.4)
45-49	62	23.7(3.2)	80.7(5.3)	73.6(14.3)
50-54	65	22.7(2.9)	79.7(5.0)	65.5(12.2)
55-59	52	22.4(2.9)	79.3(4.8)	62.2(14.7)
60-64	41	21.7(3.2)	77.9(4.7)	63.3(12.3)
65-69	25	21.8(3.0)	77.8(4.4)	52.7(14.0)
70 or over	8	20.3(1.5)	77.6(4.3)	55.6(12.1)

Figures in the parenthesis indicate the standard deviation.

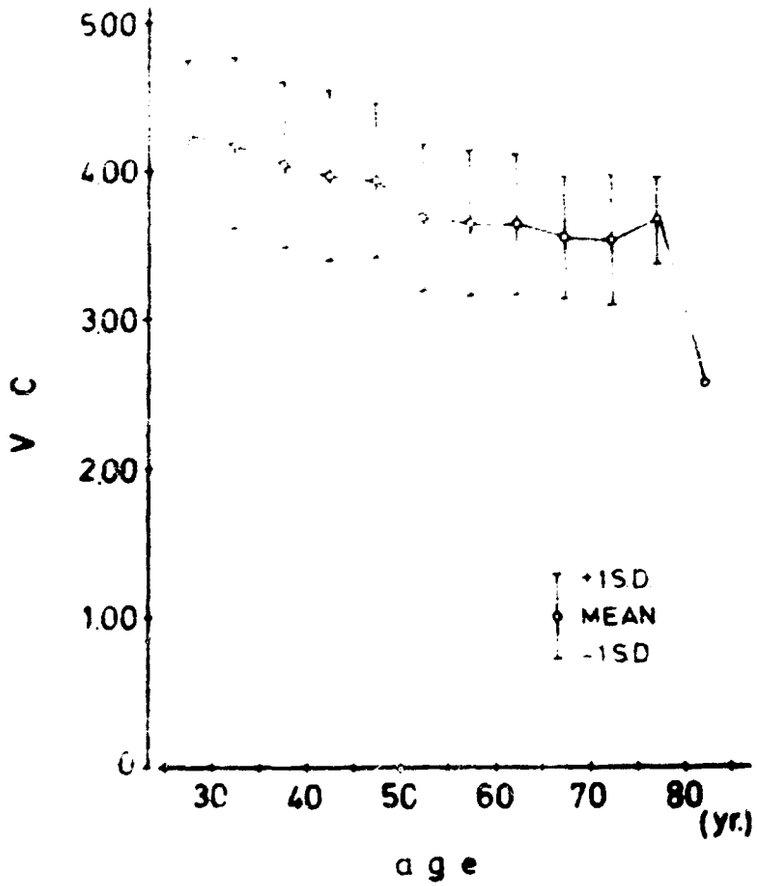

Fig.13.Vital capacity and age

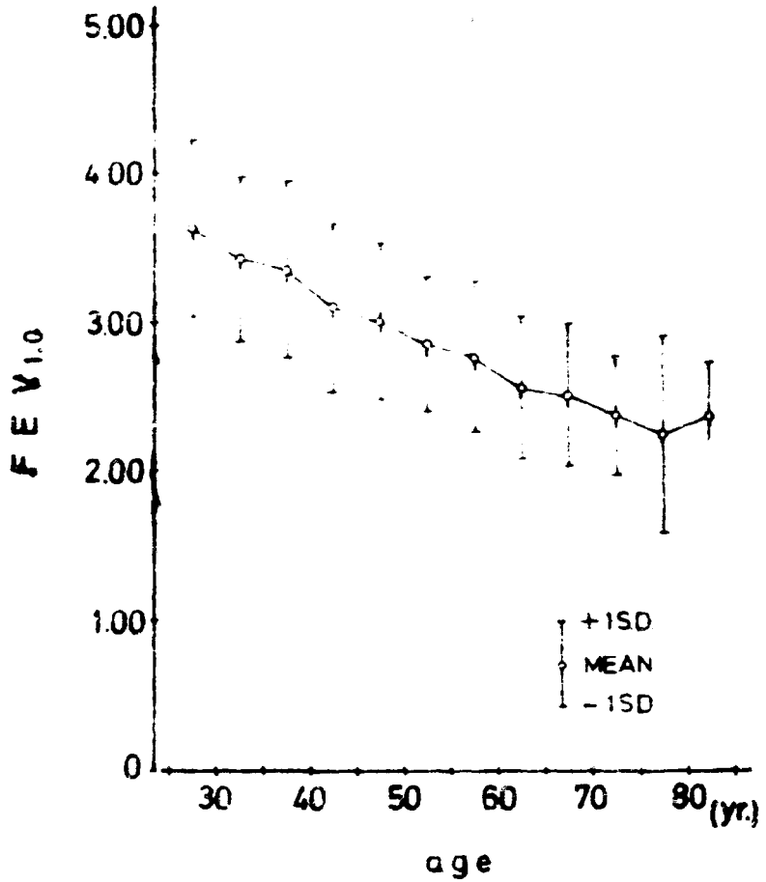

Fig.14. FEV1.0 and age

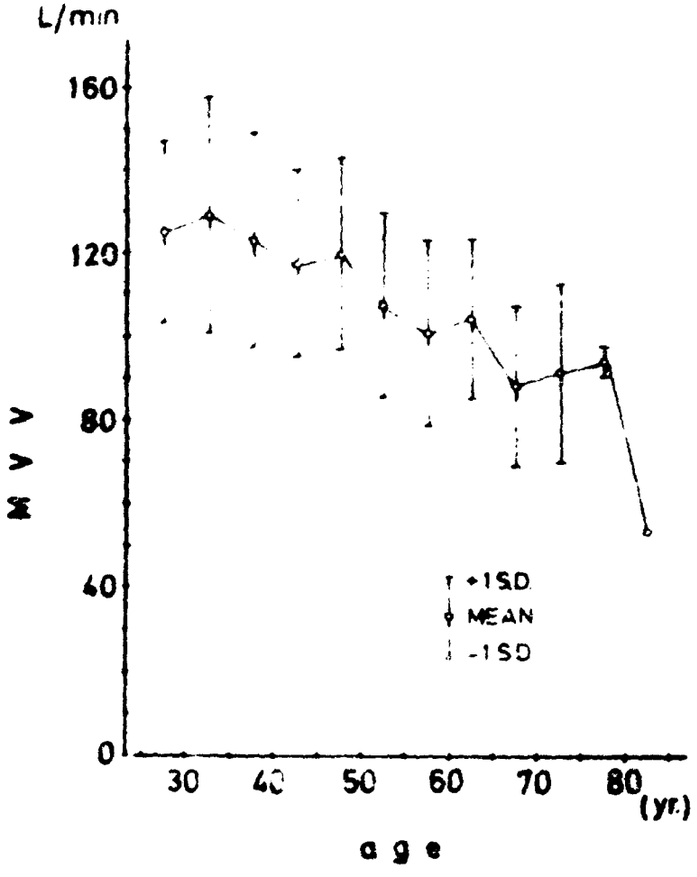

Fig.15. MVV and age

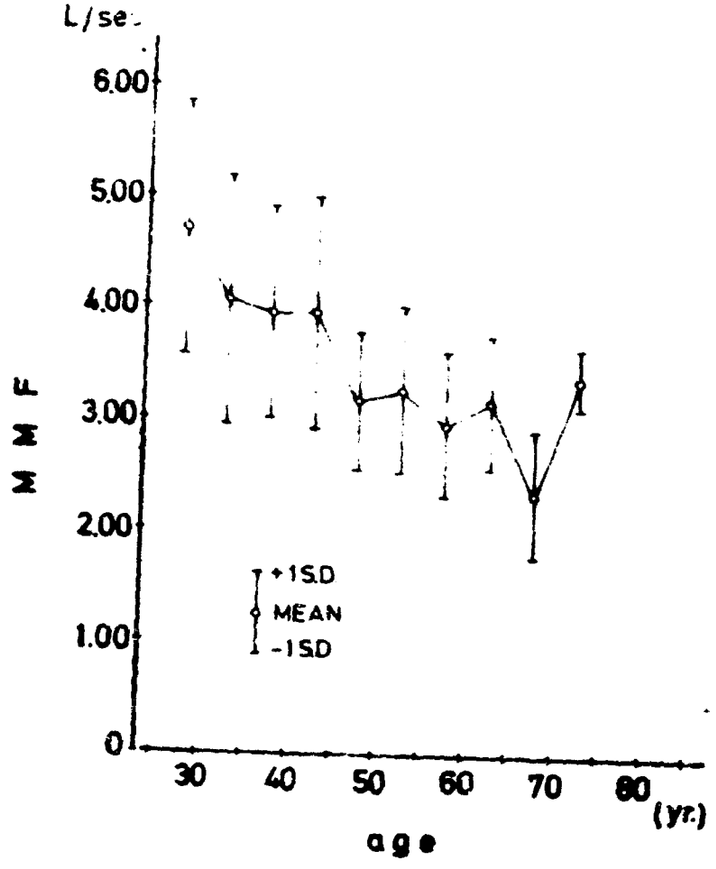

Fig.16. MMF and age

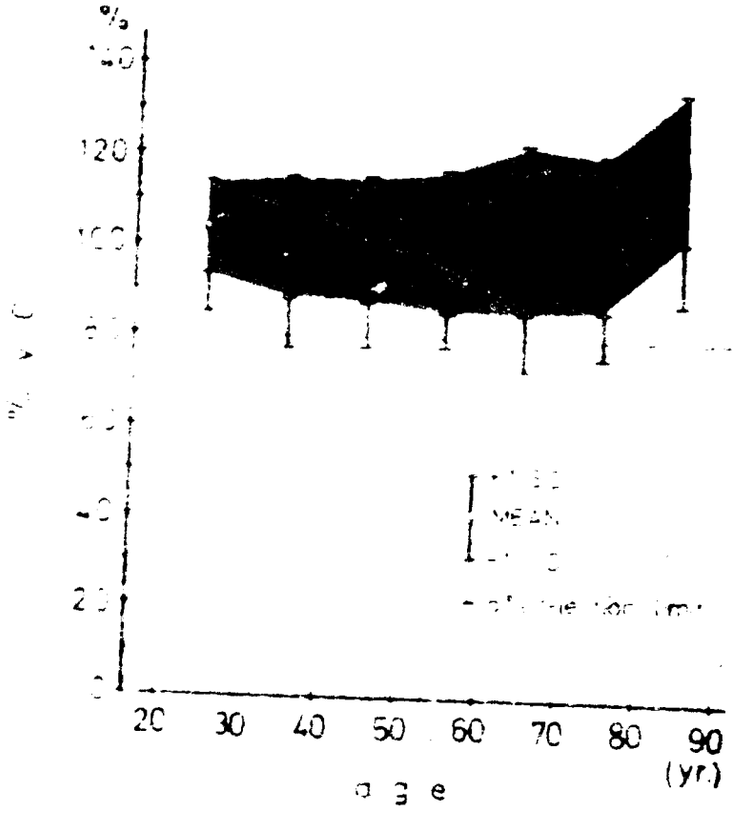

Fig.17. %VC and age

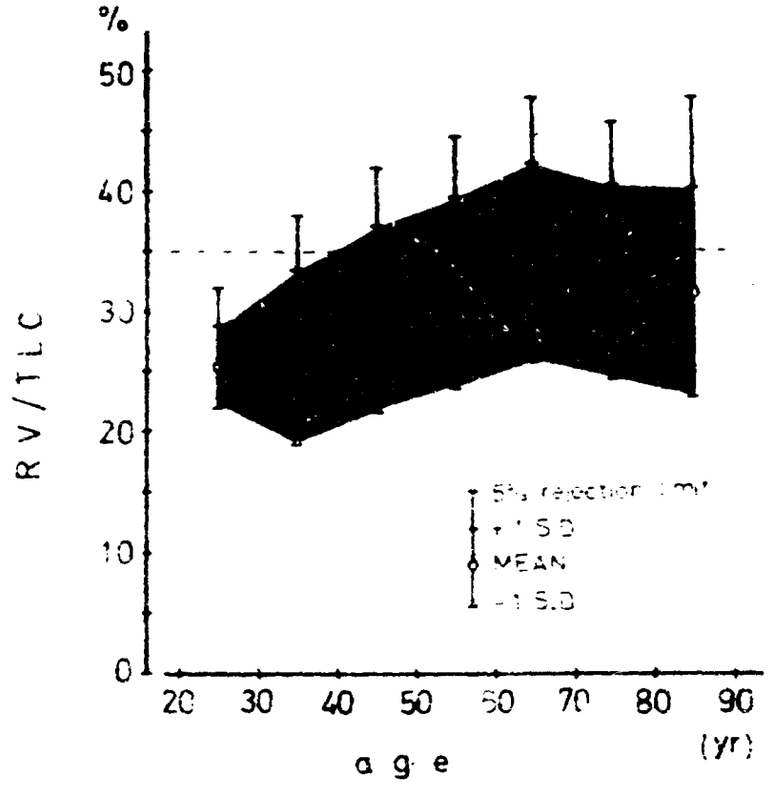

Fig.18.RV/TLC% and age

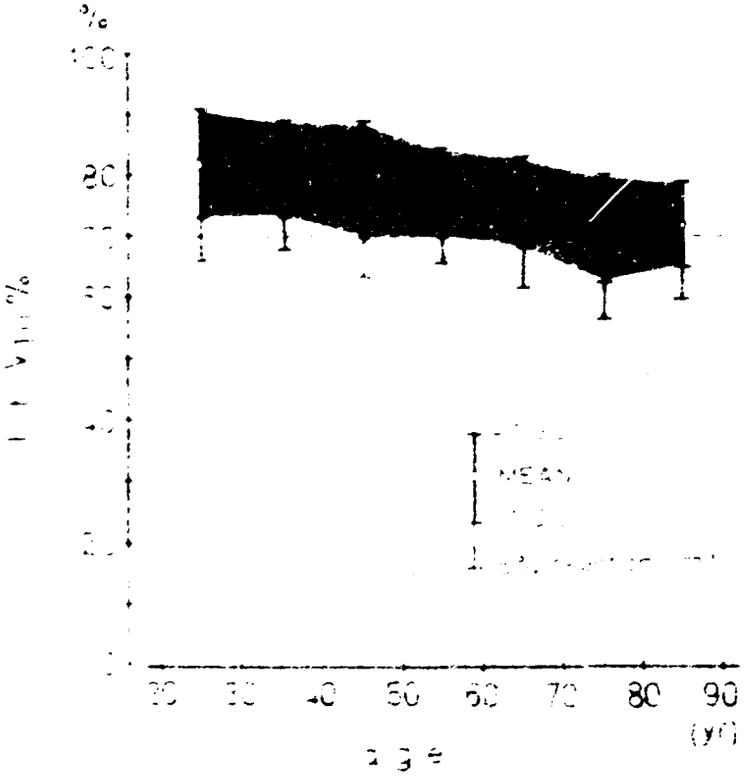

Fig.19. FEV1% and age

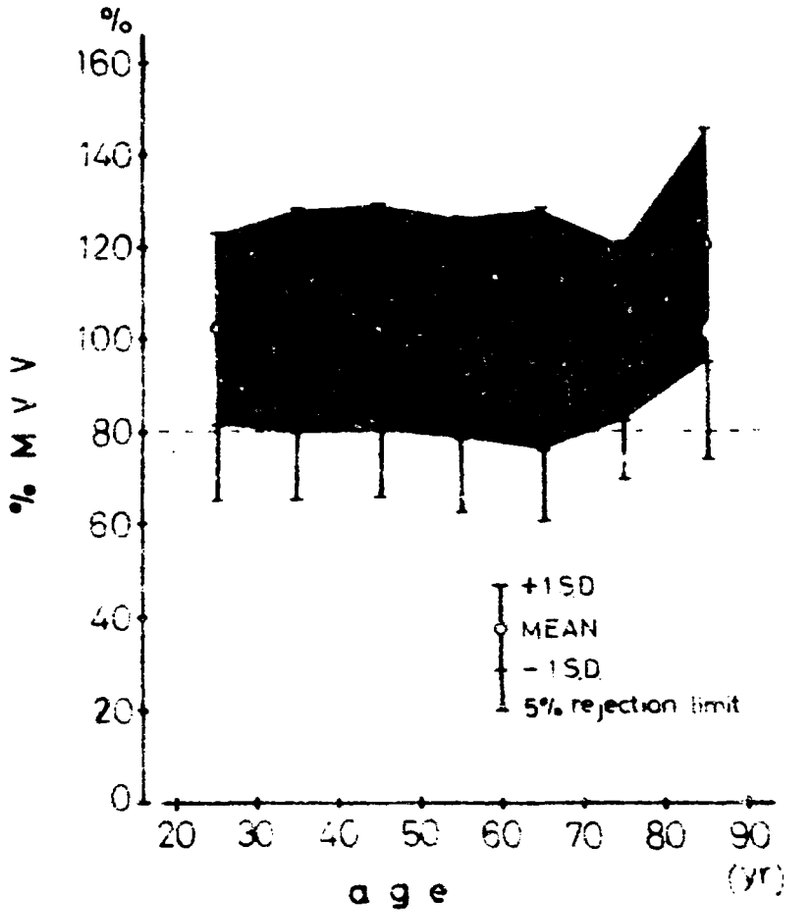

Fig.20. %MVV and age

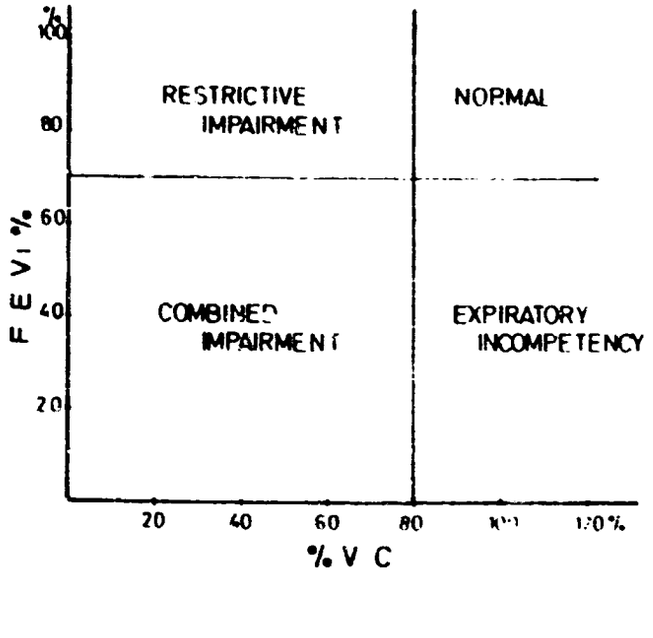

Fig.21. Classification of the impaired ventilatory capacity.

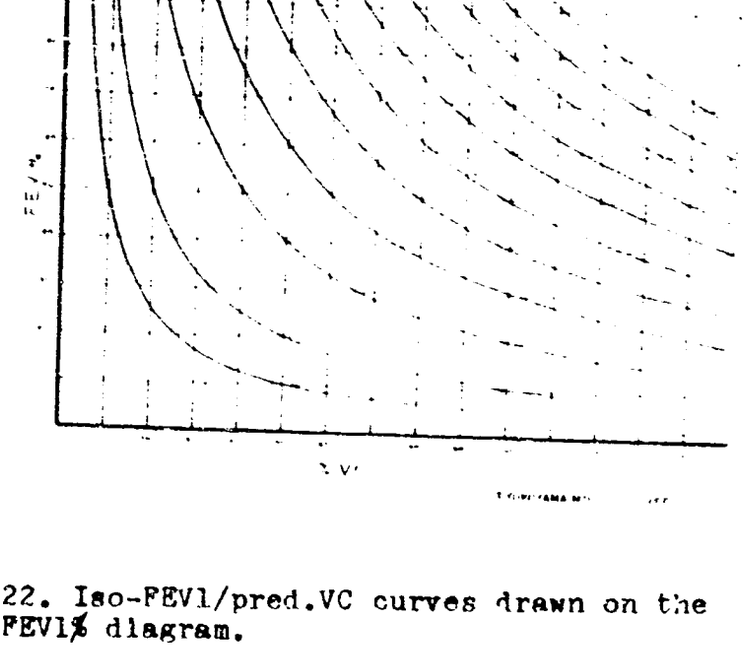

Fig.22. Iso-FEV1/pred.VC curves drawn on the %VC-FEV1% diagram.

Some parameters were related to age and sex as referred above so that we calculated the mean values in terms with sex and ages. The vital capacity was also related to the body height and the MVV to the body surface area so that the ratios of these parameters divided either by body height or body surface area were taken to find out the relationships of these parameters with age(Table 13)

The parameters, including %VC,FEV1,FEV1%,MMF and MVV on any particular age groups demonstrated normal distribution. Even though the difference in their physical constitution was eliminated the standard deviation for every parameters were found consistently larger than the corresponding values obtained in our previously reported study on the spirography repeatedly done on the limited numbers of healthy subjects.

The mathematical mean and the standard deviation for every parameters were calculated on each sex-age groups and the regression equations for the mean on these parameters in terms of age and constitutional factors were calculated. Statistical treatment was also performed on RV,FRC,TLC as well as RV/TLC ratio. The data was demonstrated in Figures 13,14,15,16,17,18,19 and 20. The calculated equations are as following.

VC(L)=0.046 H-0.012-3.29

FEV1.0(L)=0.037 H-0.022A-2.11

MMF(L/sec)=0.034 H-0.034A-0.57

MVV(L/min)=0.913 H-0.923A

RV/TLC(%)=0.203A-0.163 H+46.7

FEV1.0%=0.027 H-0.220A+84.4

(2) FEV1.0/PREDICTED VITAL CAPACITY(%):

On the clinical pulmonary function study the impaired ventilatory functions are usually classified into three major types, namely the restrictive-,the obstructive- and the combined ventilatory impairment. The restrictive ventilatory impairment is characterized by any decreased vital capacity while the obstructive ventilatory impairment

by depressed FEV1%. For the quantitative evaluation of the overall ventilatory impairment two parameters of %VC and FEV1% are used(Fig.21). Every ventilatory functions evaluated on the routine spirography may be plotted on the diagram, upon which the percent vital capacity be taken on the abscissa and FEV1% on the ordinate. Although the ventilatory impairment is thus classified one has to overcome the practical disadvantage to compare the impairment quantitatively, especially when these two parameters are not impaired in parallel. To assess the ventilatory impairment quantitatively with a single parameter we took FEV1 divided by the predicted vital capacity. Although this parameter itself does not have any definite physiological significance this reflects the changes in vital capacity as well as FEV1%. We used to take the vital capacity measured on supine position while FEV1% taken on standing position. Although the Baldwin's predicted value for vital capacity represents the value obtained on supine position. We took the vital capacity on standing position just for the convenience's sake so that the parameter of "FEV1/pred.VC" be equivalent to the product of %VC and FEV1%. This parameter of FEV1/pred.VC therefore be convenient to evaluate the overall ventilatory impairment by single parameter. Upon calculating the FEV1/pred VC% these parameters of %VC and FEV1% are thus taken equivalent to each other to represent the overall ventilatory impairment although one may not expect much physiological significance upon FEV1/pred.VC%. But on the conventional clinical diagnosis for the evaluation of ventilatory functions this parameter may be quite convenient. On the overmentioned diagram, upon which %VC was taken on the abscissa and FEV1% on the ordinate, the group of parabolic curves represent the iso-FEV1/pred.VC lines(Fig.22).

Figure 22 shows the iso-FEV1/pred.VC curves drawn at intervals on the %VC-FEV1% diagram. We have plotted the data obtained on 2423 volunteer cases upon this diagram to demonstrate the general aspects of the ventilatory functions among Japanese volunteers. Some of them revealed any impaired ventilatory functions accompanied by FEV1/pred.VC% below 60%.

(3) IMPAIRED VENTILATORY FUNCTIONS AT VARIOUS AGE GROUPS:

The incidence of the cases with any impaired ventilatory functions was studied on every age groups. Among the groups of younger adults the cases accompanied by any impaired ventilatory functions were found.

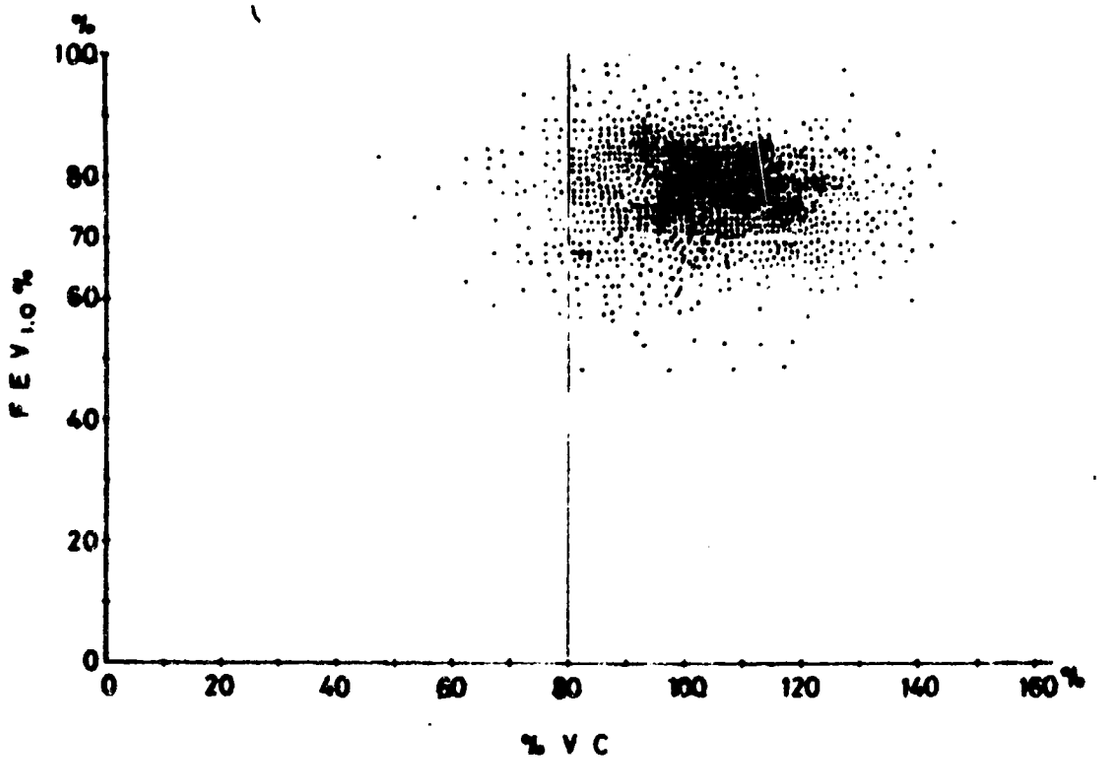

Fig.23. Ventilatory functions in 2423 volunteer Japanese subjects.

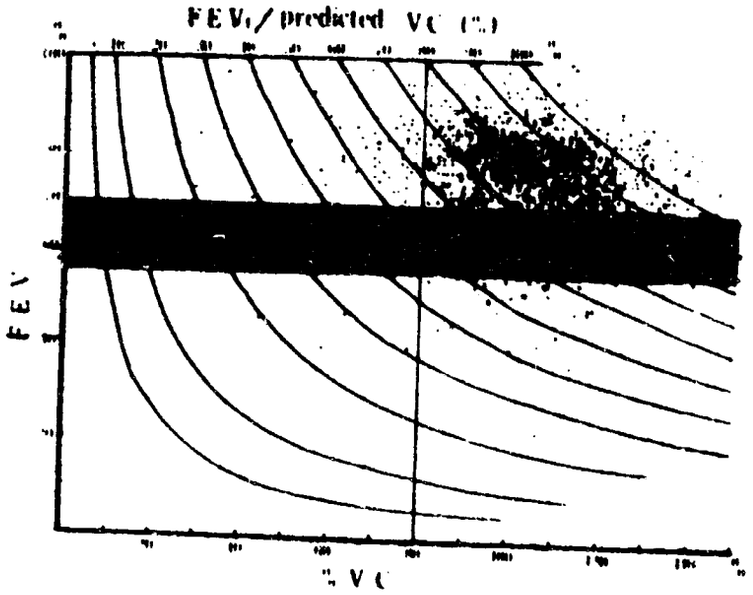

Fig.24. Ventilatory functions in 2423 Japanese volunteer subjects. Curves indicate the iso-FEV1/pred.VC lines.

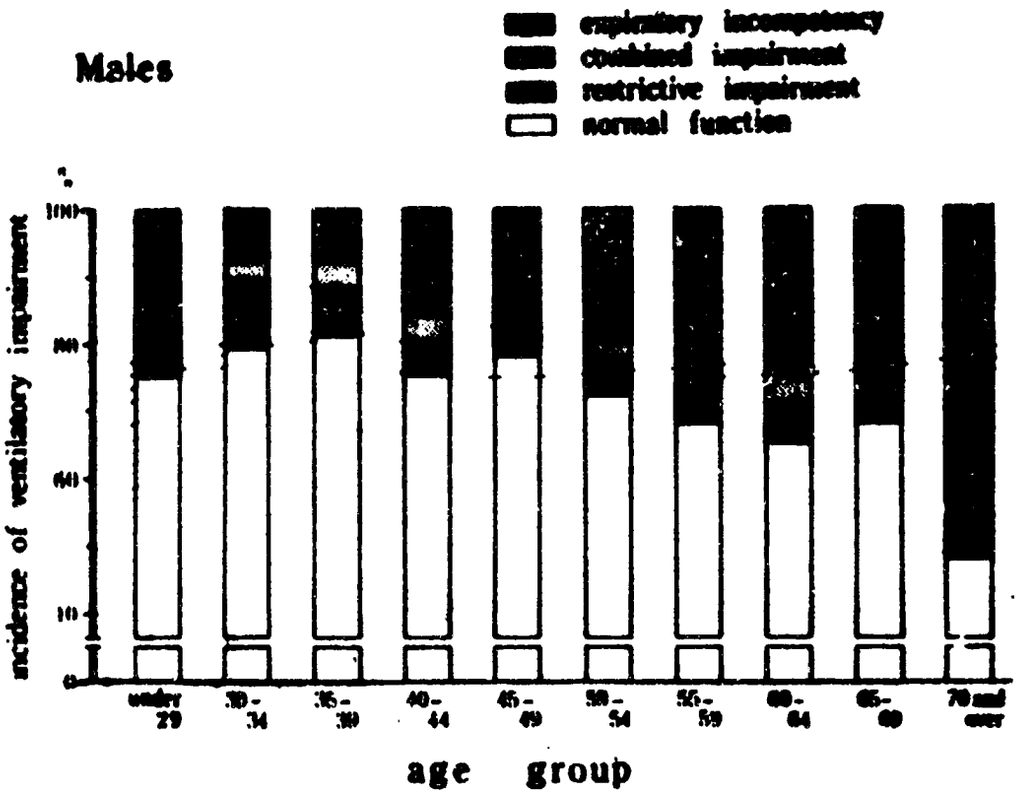

Fig.25. Incidence of ventilatory impairment among 2423 volunteer Japanese subjects

EFFECT OF AGE
ON VENTILATORY FUNCTIONS

	ventilatory changes per age	correlation coefficients with age
V C (L)	− 0.02	-0.29
$FEV_{1.0}$(L)	− 0.03	-0.52
MMF (L/sec)	− 0.04	——
MVV (L/min)	− 1.1	-0.44
$FEV_{1.0}$% (%)	− 0.2	-0.29
RV/TLC (%)	+ 0.2	+0.28

Table 14. Correlation coefficients of ventilato functions with age

EFFECT OF AGE
ON VENTILATORY FUNCTIONS

	ventilatory changes per age	
	male subjects with normal vent. functions n = 594	followed up male subjects n = 30
V C (L)	− 0.02	− 0.01
$FEV_{1.0}$ (L)	− 0.02	− 0.04
MMF (L/sec)	− 0.04	——
MVV (L/min)	− 0.9	+ 0.1
$FEV_{1.0}$% (%)	− 0.2	− 1.0
RV/TLC (%)	+ 0.2	+ 0.4

Table 15. Ventilatory changes per age

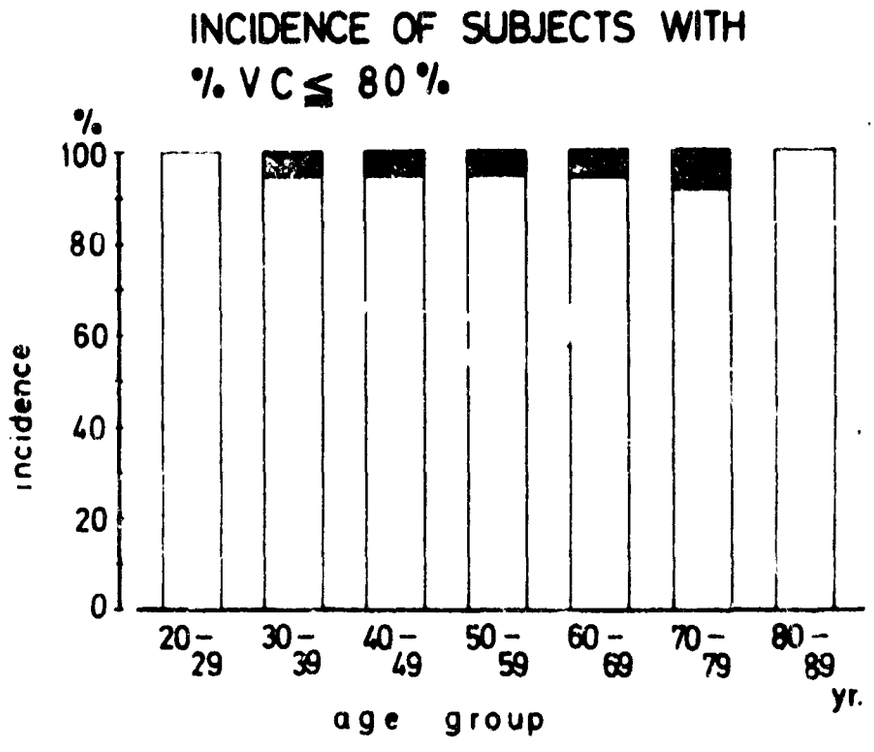

Fig.26. Incidence of subjects with %VC of 80% or less among healthy population

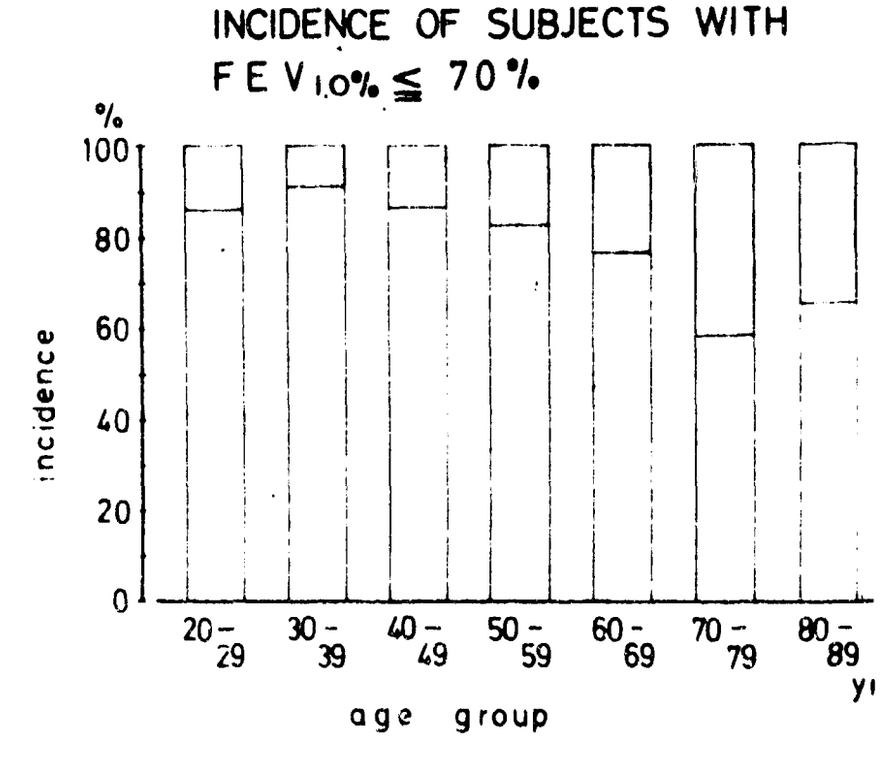

Fig.27. Incidence of subjects with FEV1% of 70% or lower in the healthy population.

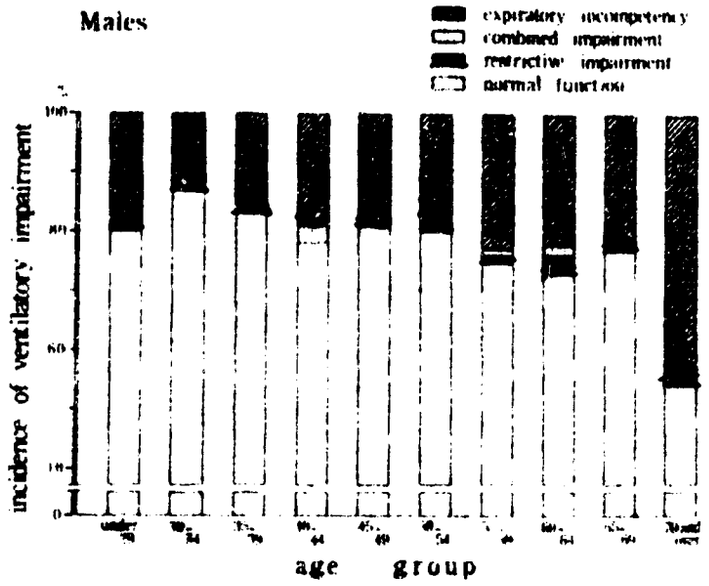

Fig.28. Incidence of ventilatory impairment among the male subjects of various ages, who did not revealed any clinical abnormality withregard to their subjective complaints, physical findings as well as to their X-ray findings on the chest.

ventilatory functions was increased as the age increased. The relative types of the ventilatory impairment was also studied. Among the aged the obstructive ventilatory impairment or the combined ventilatory impairment was rather dominant than the restrictive ventilatory impairment.

(4) FOLLOW-UP STUDIES:

The baseline studies described above was done on 2423 cases of various age groups. Question was then raised whether or not, if one picked up any particular subject to follow up, any change in his ventilatory functions may develope along the overmentioned decline of the baseline data.

We had opportunity to study repeatedly the changes in ventilatory functions by following up some particular subjects for years. The changes in every parameters per annum were calculated on these subjects of various ages.

Firstly we compared the annual changes in every parameters obtained on the followed-up healthy cases with those estimated on the different healthy subjects. The previously obtained annual rate of changes on the randomly selected healthy subjects may be represented by the value in the previously reported regression equations. Secondly we compared the annual changes in every parameters obtained on the cases accompanied by the chest diseases with those obtained on the healthy. As for the representative chest diseases accompanied by any typical ventilatory impairment we picked up chronic pulmonary emphysema and diffuse pulmonary fibrosis.

We compared the annual rate of changes for each parameters on 29 cases with chronic pulmonary emphysema and on 13 cases with pulmonary fibrosis. By comparing these annual rate of changes for these parameters any statistically consistent difference was not found. The ventilatory functions of the followed-up normal healthy changed year by year within the normal range estimated by the previously described baseline study. The cases with chronic pulmonary emphysema, whose ventilatory functions were followed up for years, revealed annual rate of changes in FEV1% without any consistent difference as compared with those in the normal healthy. But the annual rate of changes in % vital capacity on these emphysematous subjects was rather

ANNUAL VENTILATORY CHANGES

	VC (L)	$FEV_{1.0}$ (L)
followed up normals n=30	- 0.01 (+0.01 - -0.03)	- 0.04 (+0.01 - -0.09)
emphysema n=29	- 0.10 (+0.03 - -0.23)	- 0.06 (+0.02 - -0.14)
fibrosis n=13	- 0.06 (+0.02 - -0.14)	- 0.03 (+0.07 - -0.13)

figures in the parenthesis indicate 95% confidence intervals

Table 16. Annual ventilatory changes(1)

ANNUAL VENTILATORY CHANGES

	MVV (L/min)	$FEV_{1.0}$% (%)
followed up normals n=30	+ 0.1 (+6.1 - -5.9)	- 1.0 (+0.1 - -2.1)
emphysema n=29	- 2.2 (+0.2 - -4.6)	- 0.5 (+1.5 - -2.5)
fibrosis n=13	- 1.2 (+3.5 - -5.9)	+ 0.5 (+2.6 - -1.6)

Table 17. Annual ventilatory changes(2)

significant than those found in cases of normal healthy.

On the followed-up cases accompanied by diffuse pulmonary fibrosis the impaired ventilatory functions changed with the average annual rate of change equivalent to those found in the normal healthy. Although the average rate of changes in the ventilatory functions did not show any consistent difference on the cases with pulmonary fibrosis, the time-to-time fluctuation in their impaired ventilatory functions was quite larger as compared with those in the normal healthy. Statistically treated data on the parameters on the vital capacity, FEV1, FEV1%, MMF and on MVV are summarized in Tables 16 and 17.

c. CONCLUSION:

The baseline study on the ventilatory functions among Japanese population of various ages was reported. The study allowed us to establish the regression equations for the mathematical mean on the various parameters as well as to demonstrate the distribution of the data with regard to the age.

In Figures17,18,19 and 20 the 5% rejection limits calculated with regard to each age groups were indicated. Note these 5% rejection limits for FEV1% for the aged. 70% of FEV1% seems too severe for the normal limits on the aged population.

4. STUDIES ON THE AIRWAY RESISTANCE:

a PURPOSE FOR THE STUDY:

The diagnosis on so-called chronic obstructive pulmonary diseases be given basing upon the data on pulmonary physiology in addition to the patient's clinical symptoms.

Although the so-called obstructive ventilatory impairment is characterized by the depressed FEV1% on the spirography, there are some technical problems to be explored. The pulmonary function data in the routine medical practice be collected on the spirography. But the data on the routine pulmonary function tests often reveals discrepancy with the clinical findings on the asthmatic

patients as well as on the bronchitic ones. This discrepancy suggested us to conduct the present studies. We have focused our aim upon the following points to explain this discrepancy. The following points will be discussed hereunder.

The routine spirography could possibly be not sensitive enough to pick up every minor obstructive changes occurred in the airway. The second question was placed upon the diagnostic criteria. The diagnostic criteria used to evaluate the ven ilatory functions among the U.S. military personnel was too severe so that the incidence of obstructive ventilatory impairment could possibly be appeared too high. FEV1% of 80% for the diagnostic limit seems too severe. Since the repeatedly measured FEV1% demonstrate the normal distribution, if one take the mathematical mean for FEV1% as the normal limits, 50% of the total cases may be diagnosed abnormal. For the healthy young adults the mean FEV1% may be 83% with standard deviation of less than 5%. If one take 80% for the lower normal limit, one has to expect very high incidence of false positive of approximately 33% of the cases examined. Therefore one has to consider any allowance for the lower normal limit of FEV1%. We have observed in our previously reported baseline study the 5% rejection limit to be below 70%. Thirdly we have to remember the fact that neither the subjective complaints nor the physical findings cannot satisfactorily be explained by these obstructive ventilatory impairment.

To discuss these technical problems to assess the ventilatory impairment we took in their present paper two major approach. One of them was to measure the airway resistance to establish its normal limits for the Japanese population. The other was to compare these data with the spirographic data to make the physiological significance for FEV1% clear.

b. SUBJECTS:

The subjects examined in this present study include both healthy and diseased. The healthy subjects were picked up from groups of the medical doctors, the interns and of the medical students. The diseased subjects, aged from 19 to 82, were randomly picked up out of the cooperative chest patients who visited the Keio University Hospital. The total numbers of subjects were 139.

SUBJECTS

	subjective symptoms and / or history of resp. disease	objective findings on abnormal (physical findings and / or chest X-P)	F.E.V1.0%	number of subjects ♂	number of subjects ♀
group I	—	—	≧70	50	16
group II	+	—		13	5
group III	+	+		28	
group IV	+	+	70>	27	
sub total				118	21
total				139	

Table 18. Subjects for the study

These subjects were carefully examined on their history on the chest diseases, the symptoms of cough and/or phlegm, the physical findings, the chest X-ray and on the spirographic data to classify these subjects into four groups. Subjects included in the "group I" did not accompany any signs and/or symptoms suggesting any chest diseases. Subjects in the"group II" were accompanied by the history of chest diseases and/or slight subjective complaints without any physical abnormalities. Since their complaints and/or physical findings were so minor that those may possibly be included in the so-called "clinically healthy" in wide sense. The subjects included in the"groups III and IV" were the patients of chest diseases. Diseased subjects who revealed FEV1% over 70% were included in the"group III" while those who accompanied FEV1% of 70% or lower were in the "group IV".

To establish the normal values for the airway resistance statistically the healthy subjects were picked up with special care under the strict criteria. The subjects who were accompanied by any subjective complaints, if it was very slight, may sometimes be included in the "clinically healthy"subjects. In this present study excluded were such "clinically healthy" out of the "normal healthy". Those who were also excluded from in our present study were the heavy smokers whose daily cigarettes consumption exceeded 20. Among those excluded from the "normal healthy" were our research associates although these doctors were able to behave perfectly normal on their daily activities. The normal healthy selected for the study under strict criteria were 50 males and 16 females.

c.METHODS:

The spirography was done on both supine- and standing position by use of the respirometer of 13.5L Benedict-Roth type. FEV1% was calculated on the spirogram taken on the standing position. The highest value for FEV1% on the repeated spirography was taken to represent his ventilatory capacity. The airway resistance was measured by the panting method using the body plethysmo-graph of pressure type. The subjects sat in the box until he got accustomed in his very restricted environment, during this period the box temperature reached approximately constant.

Panting effort with air-flow of 0.5-1.0 L/sec at frequency of 2-3/sec was performed through the pneumo-

tachograph for 10 or 15 seconds. While the subject making this panting maneuver the electronic solenoid valve shut the airflow instantaneously. The pressure change in the body-plethysmograph, the mouth pressure to represent the alveolar pressure, and the changes in airflow were continuously recorded on the Sanborn Poly-Viso recorder. The airflow resistance for the pneumotachograph-shutter system was measured as 0.42cmH20/L.sec. The measured airway resistance was corrected with this resistance of the pneumotachograph-shutter system.

d.RESULTS:

(1) AIRWAY RESISTANCE ON 118 MALE SUBJECTS:

Table 19 indicates the data on the subject's age, the mean values for the physical constitution, the mean and the standard deviation for the spirographic data as well as their airway resistance with regard to the overmentioned classification. There were no significant difference on the background data between these four groups. The means of the airway resistance for each groups were found to be 1.24±0.25,1.48±0.27,1.77±0.5+, 3.21±1.48cmH20/L.sec,respectively. The airway resistance in the groups I and II was significantly lower than those in the groups III and IV(Table 19).

(2) NORMAL LIMIT FOR THE AIRWAY RESISTANCE:

The frequency distribution on FEV1.0, airway resistance and RawxVtg measured on 50 healthy males appeared to demonstrate the normal distribution curves. The 95% confidence interval for the airway resistance was estimated as 0.50cmH20/Lsec. The 5% upper rejection limit for normal healthy was found as 1.75cmH20/Lsec.

The airway resistance was somehow related to the thoracic gas volume. Fig.29 shows the relationship observed between the airway resistance and the thoracic gas volume. In the healthy cases with smaller thoracic gas volume the airway resistance was found larger while the healthy cases with larger thoracic gas volume revealed smaller airway resistance. As for the diagnostic parameter we therefore prefer RawxVtg rather than the airway resistance because the airway resistance was dependent to the thoracic gas volume. RawxVtg is the reciprocals for the specific conductance(Gaw/Vtg). The 5% upper rejection limit for RawxVtg obtained on the "healthy male adult"

MEAN AND S.D. ON SPIROGRAPHIC AND BODY PLETHYSMOGRAPHIC DATA IN MALE ADULTS

	group I	group II	group III	group IV
No. of Subject	50	13	28	27
Age (years)	36.9 (20~72)	43.1 (22~78)	43.8 (19~82)	55.8 (31~72)
Height (cm)	167.0 (152.0~180.5)	163.9 (159.0~178.0)	160.9 (146.2~172.0)	161.9 (153.0~170.3)
Weight (Kg)	63.5 (48.0~78.0)	63.0 (48~82)	54.8 (34.0~76.0)	53.9 (39.0~82.6)
V C (L)	4.25 ± 0.82	3.95 ± 0.67	3.29 ± 0.88	2.89 ± 0.66
FEV1.0 (L sec)	3.53 ± 0.71	3.29 ± 0.75	2.54 ± 0.72	1.46 ± 0.59
FEV1.0% (%)	84.2 ± 5.3	84.2 ± 6.3	79.1 ± 6.0	54.6 ± 12.9
MMF (L sec)	4.23 ± 1.27	4.13 ± 1.12	2.63 ± 1.04	0.89 ± 0.56
Raw (cmH2O/L sec)	1.24 ± 0.25	1.48 ± 0.27	1.77 ± 0.54	3.21 ± 1.48
Gaw (L sec/cmH2O)	0.83 ± 0.18	0.70 ± 0.11	0.60 ± 0.16	0.39 ± 0.17
Vtg (L)	3.42 ± 0.47	3.17 ± 0.48	3.23 ± 0.66	4.52 ± 1.26
Raw × Vtg (cmH2O·sec)	4.15 ± 0.41	4.55 ± 0.60	5.54 ± 1.35	14.96 ± 8.95
Gaw / Vtg (cmH2O/sec)	0.242 ± 0.036	0.220 ± 0.023	0.186 ± 0.024	0.086 ± 0.013

R_{aw} : AIRWAY RESISTANCE

G_{aw} : AIRWAY CONDUCTANCE (RECIPROCAL OF R_{aw})

V_{tg} : THORACIC GAS VOLUME (CONSIDERED EQUIVALENT TO LUNG VOLUME)

Table 19. Some basic data obtained.

CORRELATION OF R_{aw} WITH V_{tg} IN 50 NORMAL MALE ADULTS

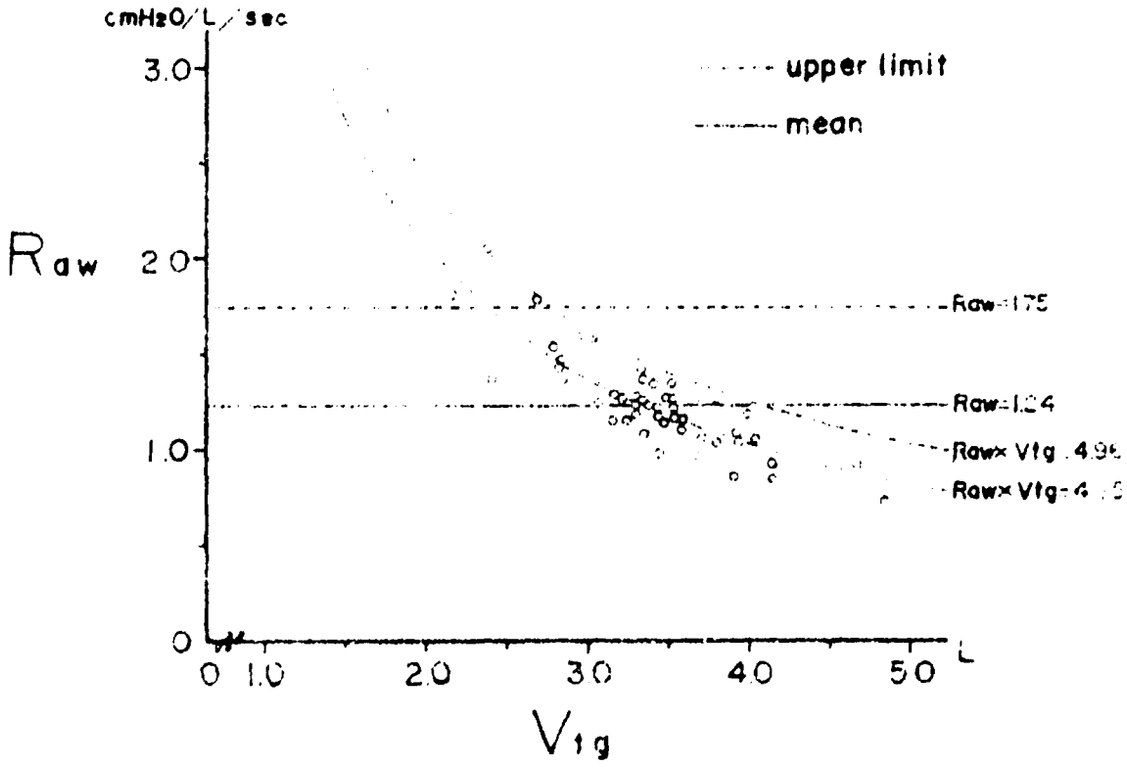

Fig.2c. Correlation of airway resistance with thoracic gas volume

CORRELATION OF R_{aw} WITH $FEV_{1.0}\%$

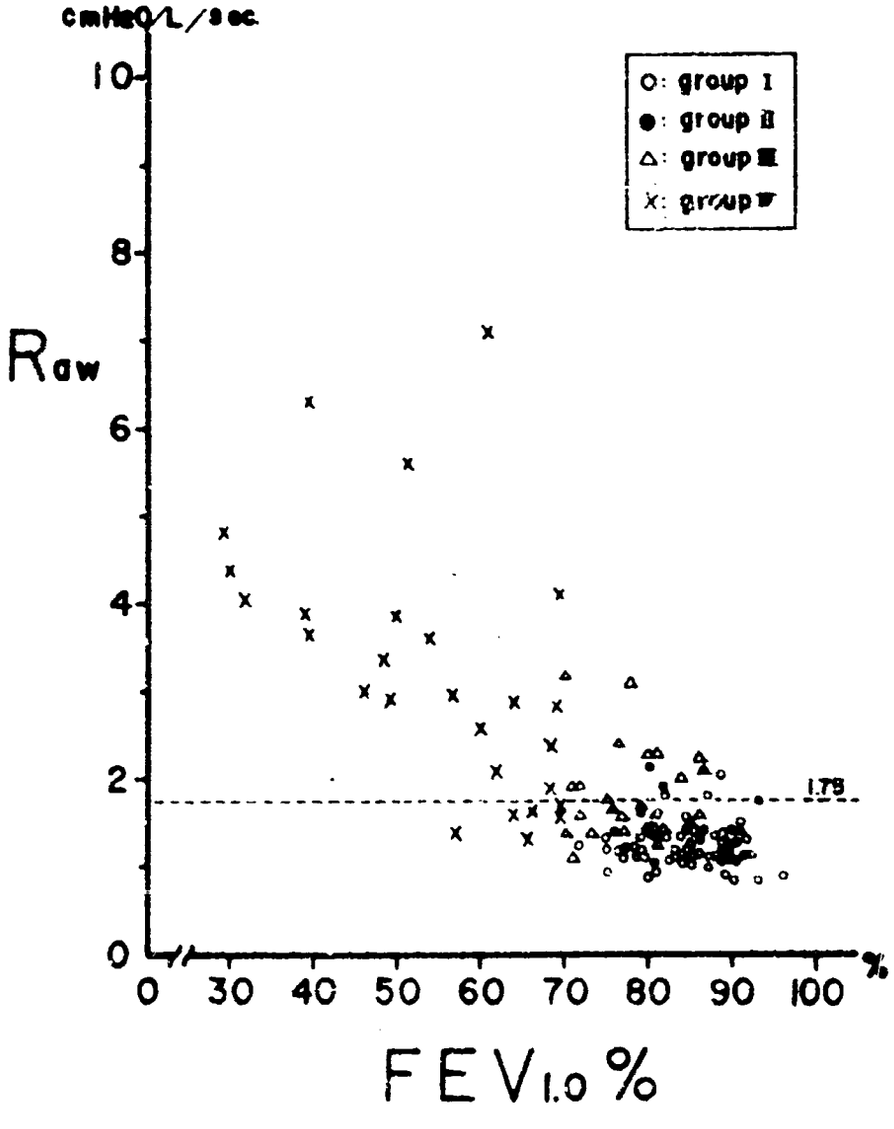

Fig.30. Correlation of airway resistance with FEV1%

was found to be 4.96cmH2Osec.

(3) FEV1% VS. AIRWAY RESISTANCE:

Relationship between FEV1% and the airway resistance is shown in Fig.30 and that between FEV1% and RawXVtg in Fig. 31 obtained on 118 cases examined. Broken lines in the figures indicate the 5% upper rejection limits. Any discrepancy in the relationship between the airway resistance and FEV1% was demonstrated. Note the fact that not every cases having abnormally increased airway resistance did revealed depressed FEV1% and that every cases with depressed FEV1% did not shown abnormally increased airway resistance. The same tendency in the relationship between FEV1% and RawX Vtg was also observed.

Further analysis was performed on the cases accompanied by FEV1% within normal limits. FEV1%, the airway resistance and RawXVtg obtained on the referring 91 cases with normal FEV1% were summarized in Fig.32. The mean values for FEV1% in the groups II and I did not revealed any statistically consistent difference, but the difference between the groups II and III was found significant.

It was interesting enough to see any statistically significant difference on the mean values for the airway resistance and for RawXVtg between the groups I and II.

Cases in the group III, accompanied by normal FEV1%, revealed increased airway resistance.

Fig.33 indicates FEV1% on 81 cases in four groups, who revealed airway resistance within normal limits. Also be noted that 6 cases in the group IV, who revealed depressed FEV1% below 70%, by definition, were accompanied by the airway resistance within normal limits.

(4) DATA OBTAINED ON THE FEMALE SUBJECTS:

21 female adults, whose ages ranged from 19 to 70, were divided into two groups. 16 subjects were included in the group I and 5 in the group II. The criteria for the groups I and II were the same as mentioned above. The summarized data obtained is shown in Table 20.

The difference of FEV1% between cases in these two

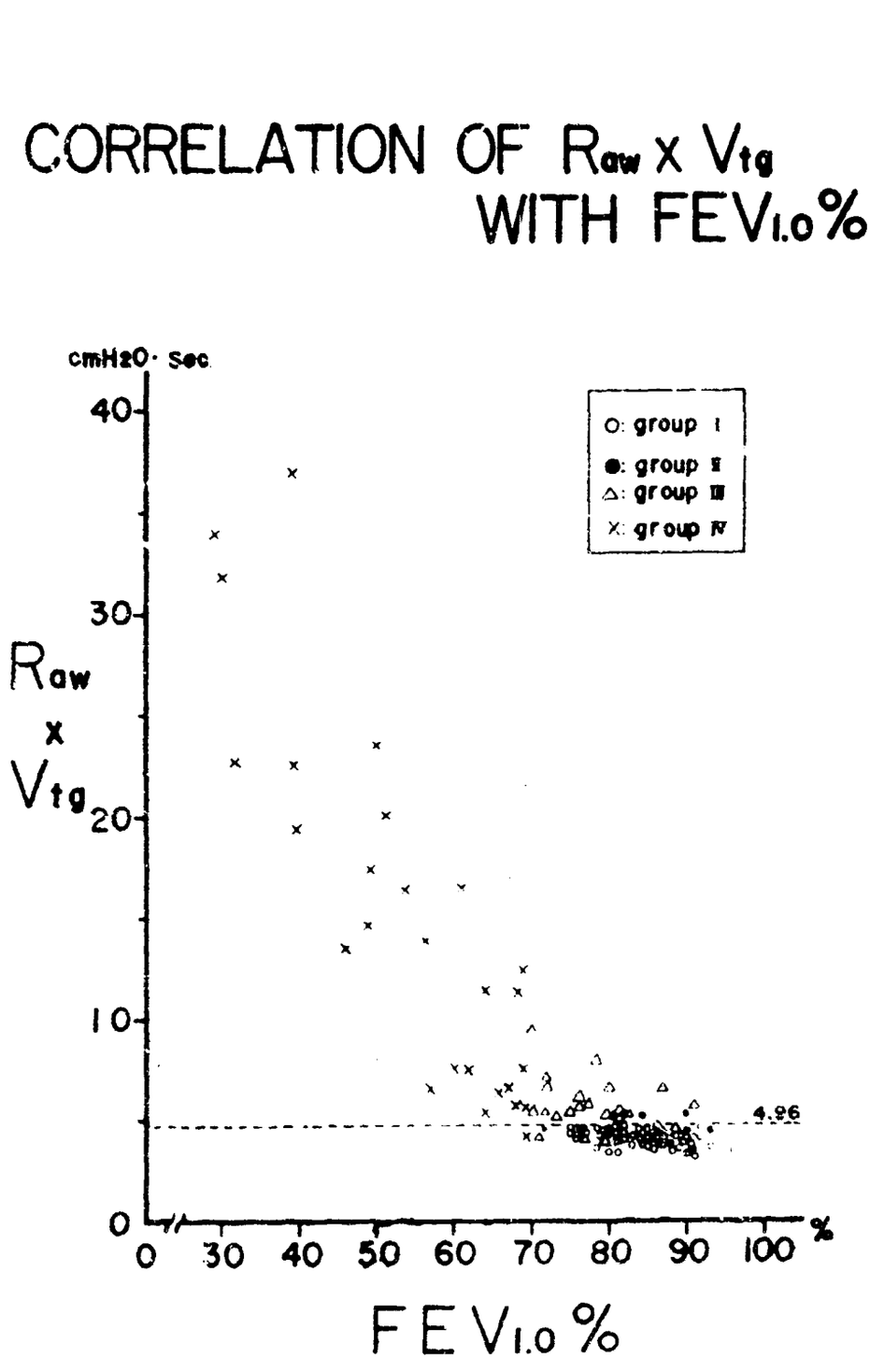

Fig.31.Correlation of RawXVtg with FEV1%

FEV1.0%, Raw AND Raw x Vtg IN GROUP WITH NORMAL FEV1.0% (MALE)

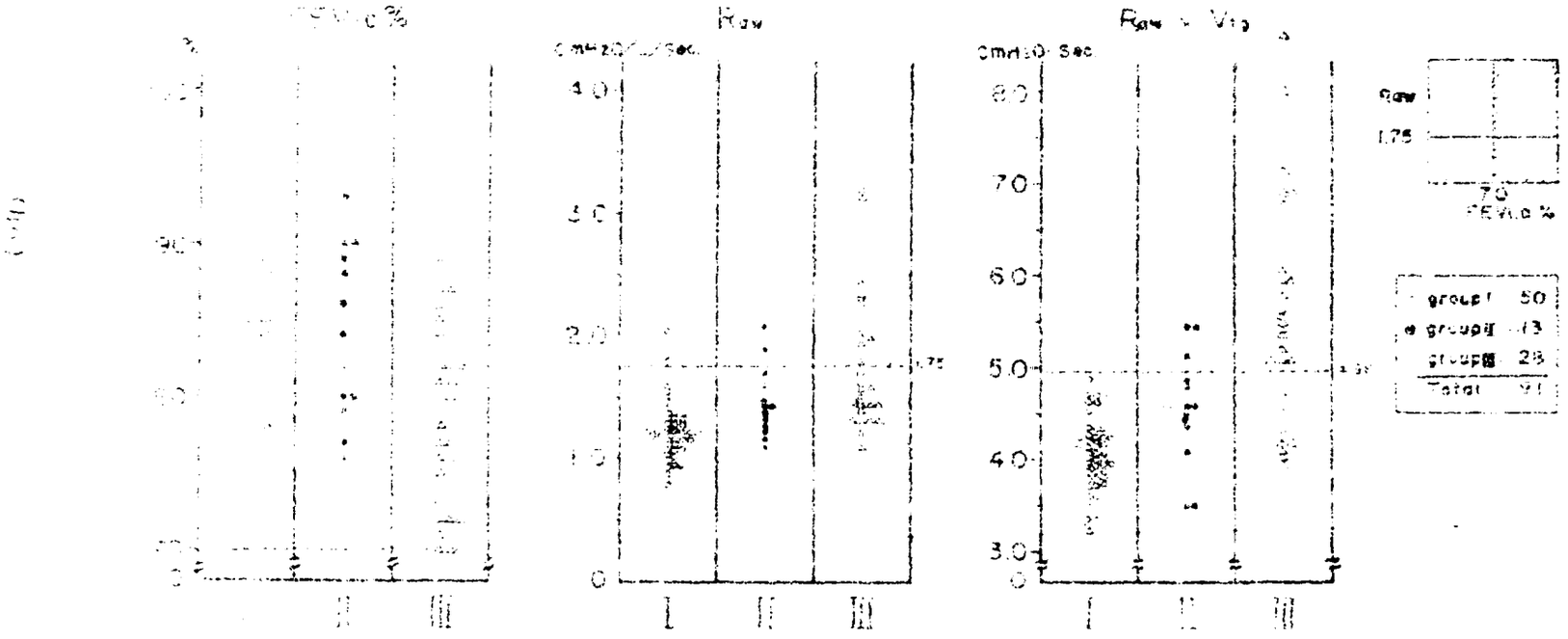

Fig.32. Airway dynamics in cases with normal FEV1%

FEV1.0% IN GROUP WITH NORMAL Raw

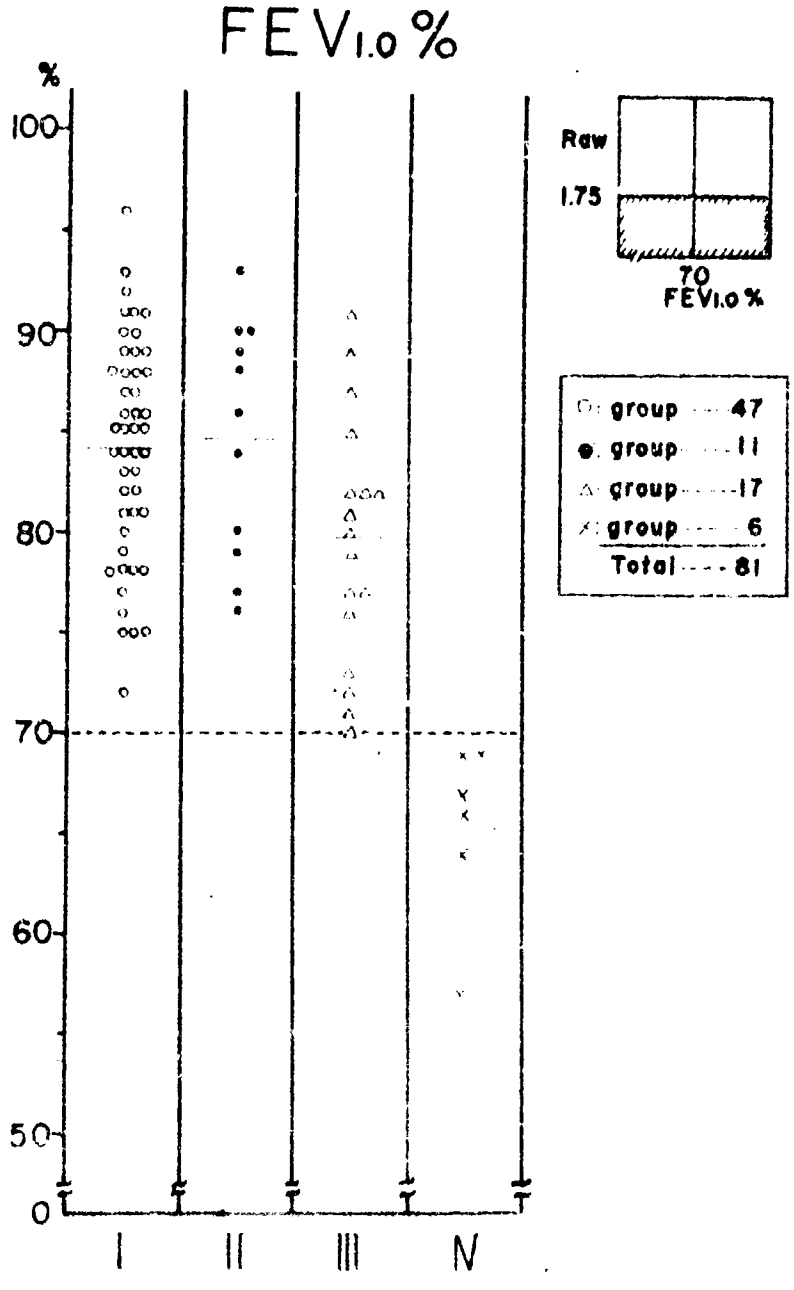

Fig.33. FEV1% in cases with normal airway resistanc

MEAN AND S.D. IN FEMALE ADULTS WITH NORMAL $FEV_{1.0}\%$

		group Ⅰ	group Ⅱ
No. of Subject		16	5
Age	(years)	33.6 (19~70)	43.6 (33~56)
Height	(cm)	155.4 (146.0~166.0)	155.2 (152.6~162.2
Weight	(kg)	52.1 (41.0~71.0)	54.8 (40.0~72.0)
V C	(L)	2.73 ± 0.43	2.84 ± 0.39
FEV1.0	(L/sec)	2.28 ± 0.41	2.29 ± 0.36
$FEV_{1.0}\%$	(%)	84.5 ± 5.1	82.4 ± 3.6
MMF	(L/sec)	2.99 ± 0.58	2.80 ± 0.63
Raw	(cmH_2O/L/sec)	1.31 ± 0.25	1.49 ± 0.22
Gaw	(L/sec/cmH_2O)	0.79 ± 0.18	0.69 ± 0.11
Vtg	(L)	2.69 ± 0.32	2.89 ± 0.42
Raw×Vtg	(cmH_2O·sec)	3.44 ± 0.87	4.21 ± 0.19
Gaw/Vtg	(cmH_2O^{-1}·sec^{-1})	0.293±0.056	0.239±0.026

Table.20. Mean and standard deviation for female adults.

FEV1.0%, Raw AND Raw x Vtg IN GROUP WITH NORMAL FEV1.0% (FEMALE)

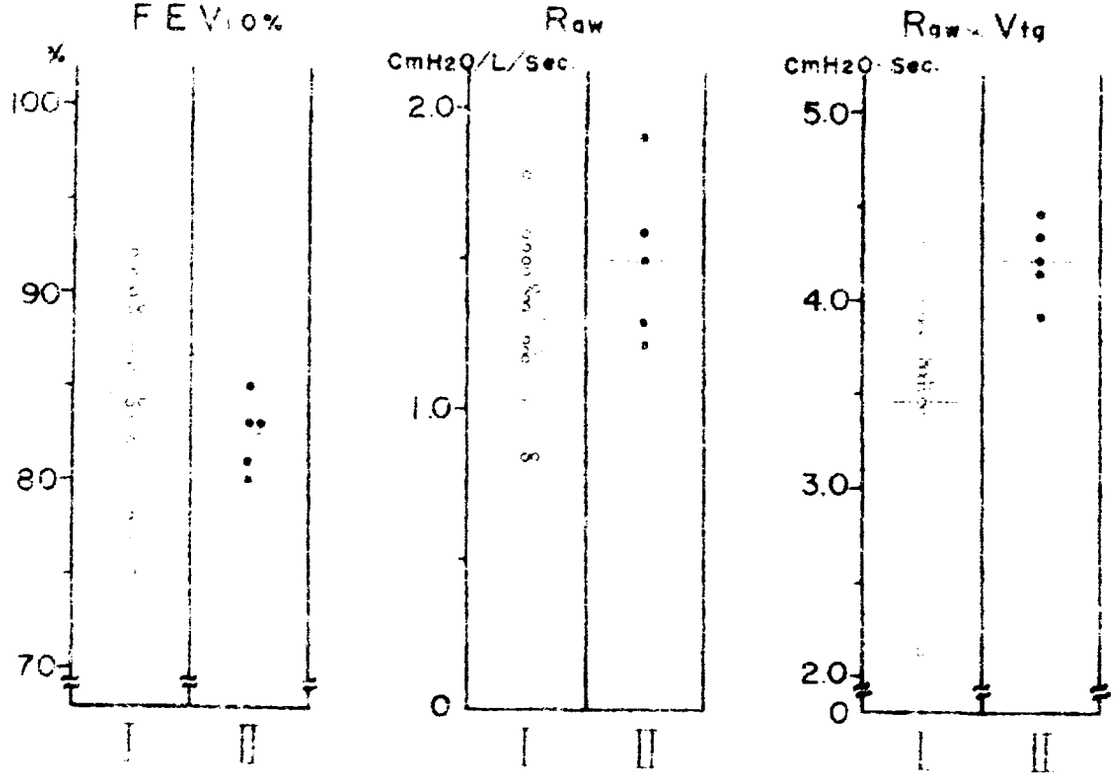

Fig.34.Airway dynamics in cases wit.. normal FEV1%

groups was not significant while those of the airway resistance as well as of RawXVtg were found statistically significant on these referring two groups.

e.CONSIDERATION:

(1) CRITERIA FOR THE NORMAL HEALTHY:

To establish the normal limits for the airway resistance one has to define the criteria for the "healthy subjects"strict. The subjects, who are able to continue their daily activities quite normal except for any slight subjective complaints of morning cough and/or phlegm production, might sometimes be included in the group of clinically healthy. But, as being demonstrated in this present paper, the clinically healthy subjects in a broad sense often revealed high airway resistance exceeding the normal limits.

Some heavy smokers were included in these groups accompanied by increased airway resistance. There are papers dealing with the airway resistance on the cigarette smokers. Jeeger and Otis excluded cigarettes smokers to establish their normal values for the airway resistance. Gayatt et al used the healthy prisoners as for the subjects for their normal values of the airway resistance so that they could exclude the direct, immediate effects of smoking. Pelzer et al studied the airway resistance on the healthy young adults. They did not found any consistent difference on the airway resistance between smokers and non-smokers although they found the difference among the aged population. For the normal FEV1% it may not be necessary to take such severe criteria for the "normal healthy" because the spirogram is not sensitive enough to pick up every minor abnormalities.

(2) NORMAL VALUE FOR THE AIRWAY RESISTANCE:

For the practical purposes upon examining the impairment the 5% upper rejection limit for the airway resistance may be much significant than the mathematical mean. We statistically treated the airway resistance obtained on 50 healthy males to calculate the 95% confidence interval for the mean as well as the 5% upper rejection limit.

The normal values for the airway resistance reported by various authors are compiled in Table 21. DuBois et al,

Mean values and standard deviation on airway resistance as measured by different authors.

authors and references	number of subjects	age mean and/or range	Raw (cmH$_2$O/L/sec)	Gaw (L/sec/cmH$_2$O)	Vtg (L)	Raw x Vtg (cmH$_2$O-sec)	type of plethysmo.
DuBois et al.[29] (1956)	22	34 (22-57)	1.50 ± 0.49		3.58		pressure
Marshall and DuBois[30] (1956)	12	31	0.79 ± 0.23	1.06			pressure
Briscoe and DuBois[4] (1958)	18 (♂ 11 ♀ 7)	(23-40) (16-87)	1.11 1.23	0.90 0.81	4.0 3.08	4.20	pressure
Butler et al.[28] (1960)	10	(75-90)	1.3	0.77			pressure
Nadel and Comroe[40] (1961)	48	29	1.14 ± 0.27	0.84	3.66	4.17	pressure
Linderholm[39] (1963)	-	35		0.76			pressure
Jaeger and Otis[25] (1964)	24	(21-49)	1.73 ± 0.42		4.24 ± 0.7		volume
Pelzer and Thomson[34] (1966)	82	46.4 (16-82)	1.14	0.88 0.32	3.96 ± 1.01	4.42	pressure
Yamabayashi[38] (1966)	20	49.8	1.7 ± 0.1			4.7 ± 0.2	volume
Tanabe et al.[36] (1966)	12	49.4	1.40 ± 0.42				volume
Duyatt et al.[31] (1967)	16	28 (21-48)	1.16 ± 0.27	1.03 ± 0.15	3.62 ± 0.24		pressure
Watanabe (1968)	84 (♂ 63 ♀ 50* ♀ 21 ♀ 16*)	37.2 (21-79) 36.3 (20-72) 36.2 (19-70) 43.6 (19-70)	1.30 ± 0.38 1.24 ± 0.36 1.26 ± 0.33 1.31 ± 0.31	0.90 ± 0.19 0.84 ± 0.18 0.77 ± 0.16 0.80 ± 0.18	3.37 ± 0.49 3.42 ± 0.47 2.74 ± 0.33 2.69 ± 0.32	4.23 ± 0.61 4.15 ± 0.41 3.62 ± 0.85 3.44 ± 0.87	pressure

* normal non-smoking subjects selected arbitrarily

Table.21. Reported airway resistance in normal healthy

discussed this particular problem on the distribution of the normal value. Although some papers concerned in discussing with the normal values for the airway resistance, were only indicated the mathematical mean with or without standard deviation. Some of the papers took the airway conductance instead of the resistance. We indicated the overall airway conductance and the specific airway conductance, which is represented by the airway conductance per unit thoracic gas volume, in addition to the previously indicated values represented by the airway resistance. The Table 22 contained our own data obtained on two types of populations, one of them was the normal healthy selected under strict criteria and the other was the normal value in a broad sense covering the value obtained on both groups I and II.

(3) VALUES AT VARIOUS AGES:

Butler et al. reported the airway resistance measured at a time of the spirography was done. Although they did not find any consistent difference in the airway resistance on different age groups although they did any consistent decrease in MVV with aging. Pelzer found no significant changes in airway resistance with age.

In an observation any spirographic changes were noticed in the population of age over 40 years But our healthy male subjects did not revealed any precise difference in the airway resistance over wide ranges of age(Table 22.

(4)RawXVtg:

The airway resistance is dependent to the thoracic gas volume maintaining hyperbolic relation. Thus the airway conductance reveals linear relation with the thoracic gas volume. The relation obtained on the normal healthy may be indicated by the following formulae.

$$RawXVtg=K \qquad (K=4.2)$$

$$Gaw/Vtg=K' \qquad (K'=0.24)$$

For the diagnostic parameter RawXVtg is considered much preferable rather rhan the airway resistance,Raw. Although 42% of the population in the groups II and III, whose FEV1% was found 70% or higher, revealed airway resistance exceeding the normal limit of 1.75cmH2O/Lsec

MEAN AND S.D. IN NORMAL ADULTS ACCORDING TO AGE

	20 ~ 29	30 ~ 39	40 ~
No. of Subject	15	18	17
Age (years)	24.5 (20~29)	33.3 (30~37)	51.6 (41~72)
Height (cm)	169.8 (162~176.0)	167.7 (152.0~180.5)	162.1 (153.5~172.0)
Weight (Kg)	61.2 (48.5~75.0)	64.0 (48.0~78.0)	65.0 (48.0~76.5)
V C (L)	5.00± 0.68	4.25± 0.57	3.57 ± 0.56
F E V1.0 (L/sec)	4.94± 0.52	3.62± 0.58	2.81 ± 0.35
F E V1.0% (%)	85.3 ± 5.0	86.2 ± 3.6	81.2 ± 5.3
M M F (L/sec)	4.86 ± 1.24	4.77 ± 0.95	3.08 ± 0.46
Raw (cmH_2O/L/sec)	1.20± 0.18	1.21 ± 0.23	1.31 ± 0.28
Gaw (L/sec./cmH_2O)	0.85± 0.14	0.86± 0.13	0.80 ± 0.14
Vtg (L)	3.48± 0.33	3.41 ± 0.65	3.38 ± 0.48
Raw x Vtg(cmH_2O·sec)	4.16± 0.45	3.99± 0.28	4.32 ± 0.43
Gaw / Vtg(cmH_2O·sec)	0.244± 0.042	0.252 ± 0.020	0.237 ± 0.029

Table 22. Airway dynamics in normal adults

while 71% of the cases were accompanied by RawXVtg exceeding the upper normal limit of 4.96cmH20sec. These facts suggest us the parameter of RawXVtg be much sensitive than the airway resistance itself to detect any minor abnormality. In another word, if one take the airway resistance, one might possibly miss any minor airway obstruction.

(5) THE DIAGNOSTIC SIGNIFICANCE:

The physiological significance of FEV1% was studied in relation to the airway resistance measured by the panting method. The measurement of airway resistance was performed on 139 adults, age distributed from 19 to 82 years.

Since the present study was performed with the aim to establish the normal limits for the airway resistance the selection of normal subjects was made strictly. The airway resistance for the normal healthy selected on the strict criteria did revealed consistent difference with that obtained for the so-called"clinically healthy" in a broad sense.

The present study was also performed to examine the physiological significance of FEV1% using the statistically established 5% upper rejection limit of the normal airway resistance. The spirography and the measurement of airway resistance using the body plethysmograph of pressure type were thus performed on 139 human subjects, including 118 males and 21 females, aged from 19 to 82 years old. Among these subjects included were 66 normal healthy who met the overmentioned strict criteria. Subjects were divided into four groups in terms of their subjective complaints, history of respiratory diseases, objective findings and their FEV1%.

f. SUMMARY:

1) The mean value and the standard deviation on the spirographic and the body-plethysmographic data were indicated.
2) On the group of 50 normal healthy selected under the strict criteria the authors were able to establish the normal characteristics for the airway resistance. The mathematical mean and the 5% upper rejection limits for the mean on the normal airway resistance were 1.24cmH20/Lsec and 1.75cmH20/Lsec,respectively. Those for the airway resistance multiplied by the thoracic gas volume(RawXVtg) were 4.15cmH20sec and 4.96cmH20sec,respectively.
3) The statistical analysis revealed a significant difference on the airway resistance as well as on the

airway resistance multiplied by the thoracic gas volume (RawXVtg) between the two groups. One of them was the group of normal healthy selected under the strict criteria and the other was the group accompanied bnly by any subjective complaints.
4) FEV1% was found not sensitive enough to detect any minor airway obstruction. Also the expiratory incompetency, represented by any depressed FEV1%, does not always indicate the increased airway resistance.

5.STUDIES ON THE ARTERIAL(OR URINARY)ALVEOLAR NITROGEN TENSION DIFFERENCE:

a.PURPOSE:

Basing upon the data reported by Phelps et al we assumed the existence of increased venous admixture like effect in bronchitic patients. The increased venous admixture-like effect was assumed to be due to the uneven ventilation-perfusion ratio distribution. The present study was performed to demonstrate the increased venous admixture-like effect in the bronchitic patients as well as to analyze the cause for this effects.

b.GENERAL DESCRIPTION FOR THE TECHNIQUE:

(1) COLLECTION OF BLOOD SAMPLES:

The subjects were requested to maintain themselves quiet on supine position. The Cournand's indwelling needle was inserted into the brachial artery under local anesthesia and then the subjects were kept relaxed for at least 30 minutes until they became steady state. While the subjects breathe air through the double-J-valve the expired gas was collected in the Douglas bag to be analyzed with the Scholander micro-gas analyzer and 10ml of the arterial blood was simultaneously collected anaerobically in the Luer-lock interchangeable syringes, which were lubricated with heparin-natrium solution in advance. The dead space of the syringe was filled with mercury.

In the present series of experiments the arterial blood gas tensions and its pH were measured with the IL meter Model 113-S2(Instrumentation Laboratory,Ltd.,U.S.A.) . The IL meter was calibrated by the heparinized whole blood equilibrated with the gas mixture of known composition in the Farhi's blood gas tonometer. Blood nitrogen was analyzed with the Beckman gas chromatograph Model GC2-A

equipped with Molecular Sieve 5A column of 6 feetX¼"o.d., Gas extraction was performed with the modified van Slyke apparatus, which was connected to the gas chromatograph system. Oxygen was absorbed in the reaction chamber of the van Slyke apparatus with the hydrosulfite alkaline solution. Residual CO2 was completely removed from with the Ascarite column and the water vapor with the Drierite column. These column were placed in the down stream of the carrier gas flow from the gas extraction system. Helium was used for the carrier gas. Temperature in the heated column-bath of the gas chromatograph was set at a little over 100C. With this system one can have the argon-free nitrogen peak on the gas chromatogram. This peak height for argon-free nitrogen was compared with that produced by the exactly same amount of blood sample equilibrated with air in the Farhi's blood gas tonometer, which was set at the temperature of 37.3C. The peak height of the gas chromatogram was used to represent the relative content of argon-free nitrogen in the specimen. Since the exactly same amount of the sample was injected into the extraction chamber with the specially-calibrated "sample-injector" and since the tonometered blood was equilibrated with the compressed air, of which the argon-free nitrogen tension is known, one can calculate the arterial argon-free nitrogen tension using the ratio of peak height for the arterial blood and that for the tonometered blood. In this calculation of the arterial nitrogen tension the solubility coefficient of argon-free nitrogen for blood was not necessary.

Alveolar nitrogen tension was calculated with the alveolar equation. The gas analysis data of the expired gas was used for this purpose.

(2) COLLECTION OF URINARY SPECIMEN:

Firstly the subjects were requested to empty their urinary bladder. The subjects remained seated quietly for at least 30 minutes after they took 500 ml of water.

The subjects were then passed the urine into the bottle, which contained liquid paraffin layer to separate the urine from the contamination of atomospheric air. Through thick film of this liquid paraffin the urinary specimen was transferred anaerobically into the lubricated 20ml syringe to be stored until it was analyzed. The procedure was taken as soon as possible to avoid the diffusion-loss of

of nitrogen into the liquid paraffin. The clean syringes were lubricated with saturated lithium chloride solution. The syringes filled with the specimen were stored in the ice box until the samples were analyzed. A part of this urinary specimen was used to equilibrate with the compressed air in the Farhi's blood gas tonometer to be used to obtain the calibration peak on the gas chromatogram.

We have examined the possibility of taking some "known" solubility coefficient to calculate the arterial or urinary nitrogen tension instead of using these equilibrated specimen. If this procedure be satisfactory of getting enough accuracy one can expect tremendous advantage to simplify the analytical procedures for the arterial nitrogen tension. To calculate alveolar nitrogen tension it may not be necessary to collect the expired air for analysis if we can assume the value for gas exchange ratio. Also to calculate the alveolar nitrogen tension we have to have the alveolar(or arterial) CO2 tension. If we can substitute any tentatively assumed value for this alveolar CO2 tension it maynot be necessary to perform the arterial puncture. We have examined to calculate any possible error brought up by taking these assumed values for the gas exchange ratio as well as for the arterial CO2 tension. If any allowance for the final value is expected one may tentatively substitute the estimated value either for the gas exchange ratio or for the arterial CO2 tension. But we reached the conclusion that upon calculating the arterial nitrogen tension the estimated nitrogen solubility might finally cause any prreciable error for the calculated nitrogen tension, which eliminates the diagnostic value of arterial alveolar nitrogen tension difference.

But these procedure to take the assumed values upon calculating the arterial-alveolar nitrogen tension difference with minimal errors the tremendous advantage in the population survey is expected.

c. RESULTS:

The arterial avleolar nitrogen tension difference was measured on three independent groups of subjects having different pulmonary diseases. One of them was the group of "healthy" subjects. The second group was the subjects accompanied by the episode of bronchial asthma. The other group was the subjects with typical chronic pulmonary emphysema(Fig.35).

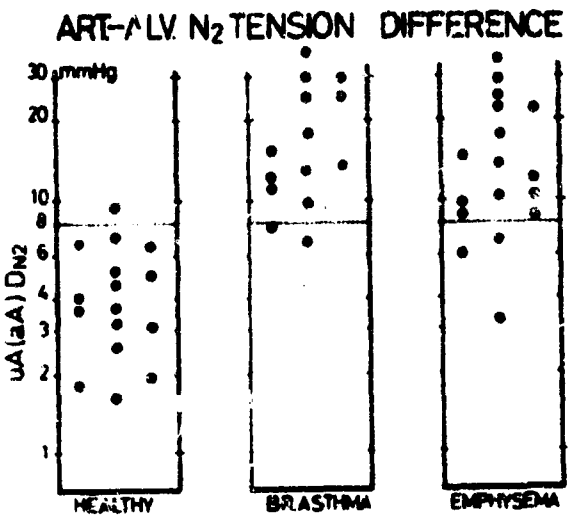

Fig.35. Arterial-alveolar nitrogen tension difference.

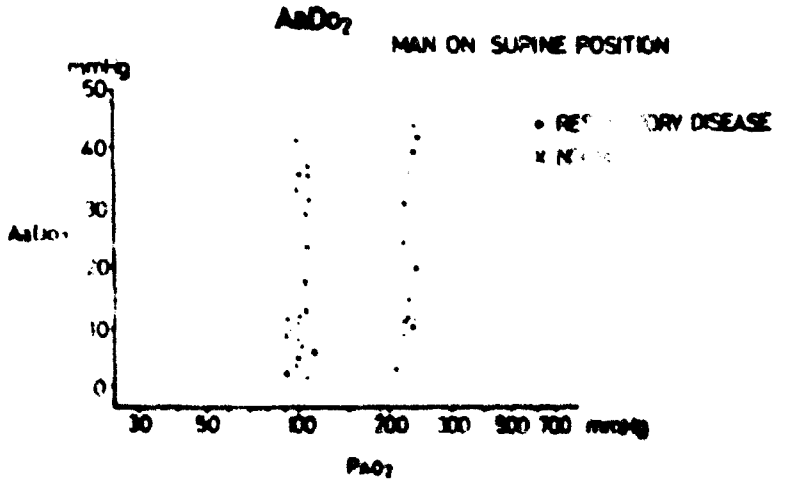

Fig.36. A2D02 on 20% and 40% 02 levels

The healthy subjects revealed their aA nitrogen difference less than 10 mmHg. Some healthy subjects revealed negative aA nitrogen difference. The unavoidable limitation on the accuracy of the analytical procedure possibly produce this negative difference.

The mathematical mean and the standard deviation for the arterial-alveolar nitrogen tension difference on the normal healthy were 3.5mmHg and 2.8mmHg, respectively. Statistically calculated 5% upper rejection limit was found to be 9.6mmHg. Based upon these data we have set the normal limit for the arterial alveolar nitrogen tension difference to be 10mmHg.

In cases with chronic pulmonary emphysema and with episodes of bronchial asthma this arterial-alveolar nitrogen tension difference was found increased. The data obtained are shown in the Fig.35.

6. STUDIES ON THE IMPAIRED ALVEOLAR GAS EXCHANGE: AaD AND PULMONARY DIFFUSING CAPACITY:

a. PURPOSE OF THE STUDY:

On the pulmonary function study to evaluate the impaired alveolar gas exchange the CO pulmonary diffusing capacity is performed routinely.

In cases with Tokyo-Yokohama asthma the arterial desaturation was pointed out and this suggested us the existence of increased venous admixture-like effect.

We have now the parameter of aADN2 as well as AaDO2 to assess the uneven ventilation-perfusion ratio distribution. The present study was designed to establish the physiological significance between these parameters of AaDO2 and aADN2 as well as between aADN2 and DLco.

Through this analysis it was also anticipated to clarify the impaired alveolar gas exchange in patients with some chest diseases.

b. METHODS AND MATERIALS:

AaDO2 at two different inspired O2 concentrations of

20% and of 40% as well as aADN2 on the air-breathing level were measured on the healthy subjects and the patients with chronic pulmonary diseases. The pulmonary diffusing capacity for carbon monoxide by the breathholding method was also measured on these subjects at a time. Routine measurement of the pulmonary diffusing capacity was performed on the supine position. The arterial puncture was made into the brachial artery with the Cournand's indwelling needle under local anesthesia. The subjects were maintained for at least 30 minutes to make him steady state, during this period he was asked to get accustomed to breathe through the double-J-valve in the open circuit system.

While the subject was kept under steady state the expired gas was collected in the Douglas bag, during which period the arterial blood was withdrawn anaerobically into the heparin-lubricated syringes. The arterial 02 and C02 tensions as well as pH were measured promptly after collection of blood samples with the I.L.meter Model 113 S-2, which was calibrated with the blood equilibrated in the Farhi's tonometer with the gases of known composition. The expired gas was analyzed with the Scholander micro-gas analyzer. The alveolar 02 tension was calculated with the alveolar equation.

After the tests at the room air level the inspired gas was switched to the 40% 02 mixture. Breathing the gas mixture for approximately 30 minutes the same maneuvers mentioned above was repeated to measure the AaD02 at 40% 02 level.

c.RESULTS:

AaD02 for the normal healthy under the room air level was measured and was found to be less than 10mmHg while those under the 40%02 level revealed relatively larger values of less than 20mmHg. The pulmonary diffusing capacity on the normal healthy was found as the mean values of 20.6ml/min.mmHg.m^2, ranging from 15.8 to 27.4ml/min.mmHg.m^2.

The present study aimed not only to obtain the base-line values for these three AaD's and for DLco, but also to analyze the impairment of alveolar gas exchange existed in cases with chronic diffuse pulmonary diseases in terms of the combination of AaD's and the pulmonary diffusing capacity. As shown in the schematic diagram AaD02's and aADN2 are influenced by some physiological

TRIPLE AaD & ALVEOLAR GAS EXCHANGE

		$AaDo_2$			$aADo_2$	aAD_{Dc}
		AIR	100% O_2	LOW O_2		
VENOUS ADMIXTURE		+ +	■	+	○	○
DIFFUSION LIMITATION		+	○	■	○	○
UNEVEN V_A/Q	HIGH $\dot{V}_A/Q$	+ +	+	+	■	○
	LOW $\dot{V}_A/Q$	+ +	+	+	+	■

Fig.37. Triple AaD and alveolar gas exchange

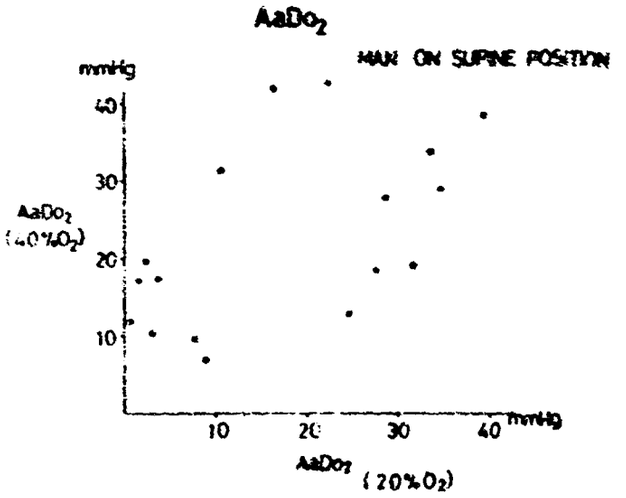

Fig.38. AaD02 on 20%02 level vs.AaD02 on 40%02 level. Subjects: men on supine position.

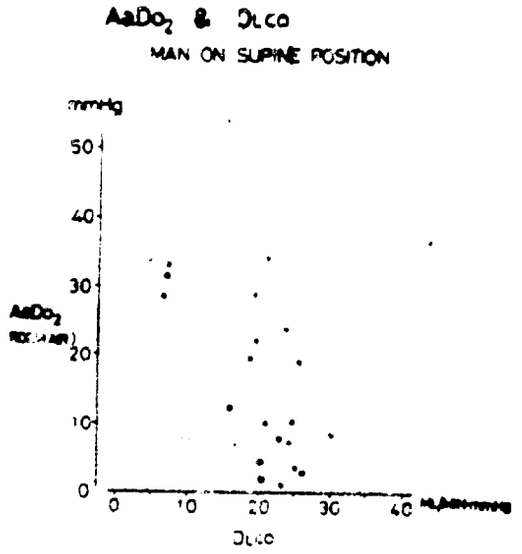

Fig.39.Pulmonary diffusing capacity vs.AaD02 on room air level

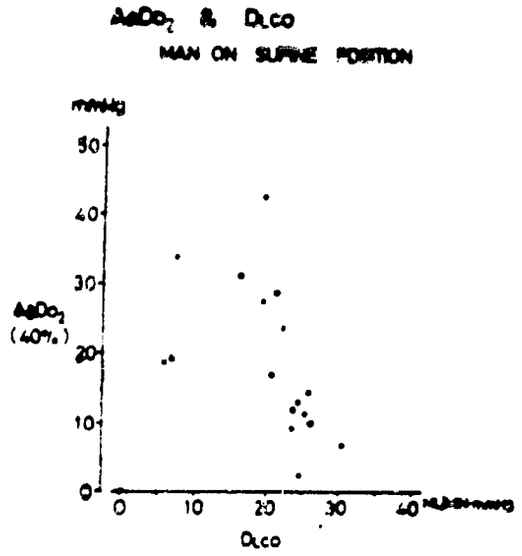

Fig.40. Pulmonary diffusing capacity vs.AaD02 on 40% 02 level

factors, such as the shunt, the diffusion barrier and the uneven $\dot{V}A/\dot{Q}$ distribution. AaD02 at the room air level is influenced by these factors. aADN2 is dependent only to the $\dot{V}A/\dot{Q}$ uneveness while AaD02 at the higher 02 level mainly depends upon the low $VA/\dot{Q}$ component as well as upon the shunt. We were also interested from some clinical point of view to analyze the contribution of these impairment upon the CO pulmonary diffusing capacity measured by the breath holding method.

Neither AaD02 on the room air level nor that on the 40% 02 level revealed straight correlation with the pulmonary diffusing capacity although the data indicated any correlation between these parameters. aADN2, which may respond only to the uneven VA/Q distribution, demonstrated somehow consistent correlation with the pulmonary diffusing capacity. Thus we could conclude that the depressed pulmonary diffusing capacity measured by the breathholding method did not directly represent the impaired diffusion, but may also be influenced by the uneven ventilation-perfusion ratio distribution. On the clinical pulmonary function laboratory this pulmonary diffusing capacity is often used to evaluate the overall alveolar gas exchange. Although the pulmonary diffusing capacity may indicate the overall functions for alveolar gas exchange it seemed to have little value to make any further analysis on the impaired alveolar gas exchange with this single parameter of the pulmonary diffusing capacity.

Apart from some physiological point of view we are to discuss some diagnostic problems limitedly concerned to the routine clinical practice. We have studied the pulmonary physiology in the bronchitic patients and found that some cases with bronchitics revealed increased aADN2 even though they were accompanied by FEV1% within normal limits.

The relation between the ventilatory functions and the ventilation-perfusion ratio uneveness will be discussed hereunder. In the Fig.41 FEV1/% was taken on the abscissa to represent the obstructive ventilatory impairment and aADN2 was on the ordinate to represent the $\dot{V}A/\dot{Q}$ uneveness.

AaD02 on the 40% 02 level was mainly dependent upon the venous admixture-like effect, including the shunt effect and the ventilation-perfusion uneveness, while aADN2 was only dependent on the uneven ventilation-

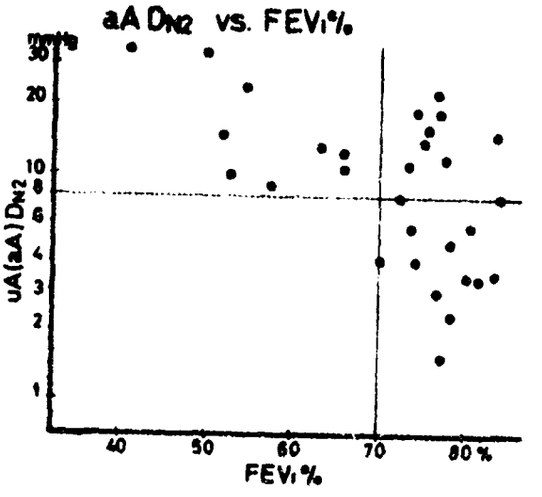

Fig.41.arterial-alveolar nitrogen tension difference vs.FEV1%.

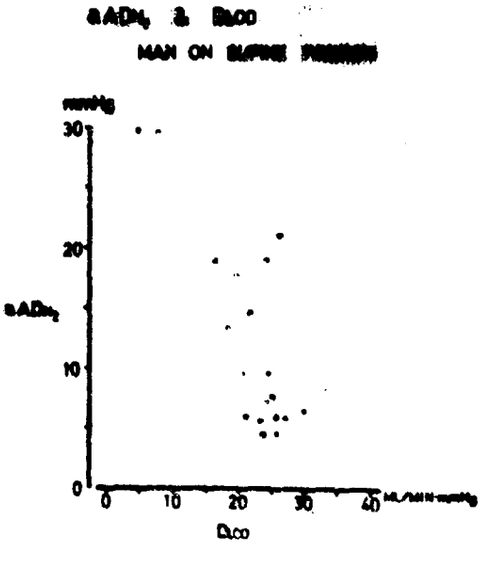

Fig.42.aADN2 vs.pulmonary diffusing capacity

perfusion ratio distribution.

With the combination of these parameters of AaD's and DLco one could possibly be able to assess the contribution of variable factors upon the impaired alveolar gas exchange. AaD02 both on the air level as well as on the 40% 02 level tended to increase up to 45 mmHg in cases with chronic pulmonary diseases. But changes in these AaD02's obtained on any particular patients was not in parallel. In cases of the normal healthy as well as those with the diffuse pulmonary fibrosis AaD02 on the 40% 02 level was larger than that obtained on the air level. In cases with chronic pulmonary emphysema AaD02 at 40% 02 level was far larger than those on the room air level. If one take the ratio between AaD02 at 40%02 level and that at room air level, the ratio in the emphysematous patients were larger than that obtained in the cases of healthy and of pulmonary fibrotics.

This seems to indicate the role of predominant venous admixture effect as well as the diffusion impairment in cases with diffuse pulmonary fibrosis and the significant uneven ventilation-perfusion ratio distribution in emphysematous patients.

On bronchitic cases accompanied by the long-term sputum production the relation between AaD02 and aADN2 was studied. AaD02 at room air level and aADN2 appeared to show somewhat linear relationship while AaD02 at 40% 02 level demonstrated rather disturbed relationship with aADN2. The fact may be explained by the contribution of the venous admixture which includes the factor independent to uneven $\dot{V}A/\dot{Q}$ distribution, at variable degree upon AaD02 at 40% 02 level in these chest patients.

AaD02 either on the room air level or on the 40% 02 level with the pulmonary diffusing capacity revealed reverse correlation while in cases with chronic pulmonary emphysema these parameters indicated somewhat disturbed relationships. In those with pulmonary emphysema the pulmonary diffusing capacity did not demonstrated any precise decrease while significantly increased AaD02's were found. It may be possible to introduce the conclusive comments as following: The pulmonary diffusing capacity measured by the breath-holding method does indicate the overall impairment of alveolar gas exchange although it seemed difficult to make any further analysis only by this pulmonary diffusing capacity.

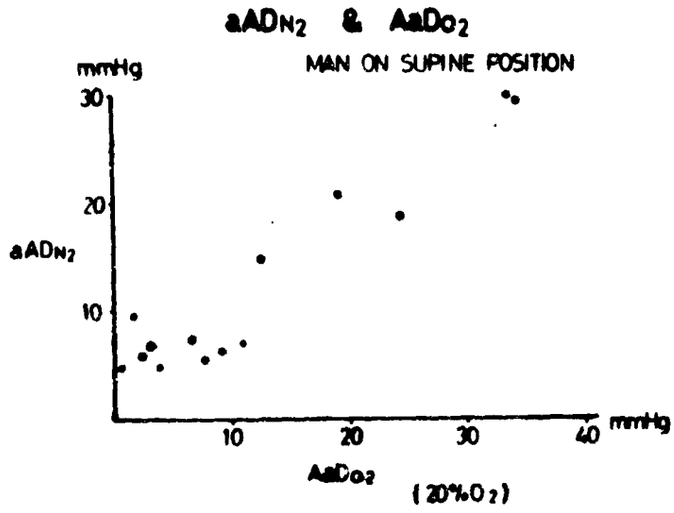

Fig.43. aADN2 vs.AaD02 on 20%02 level

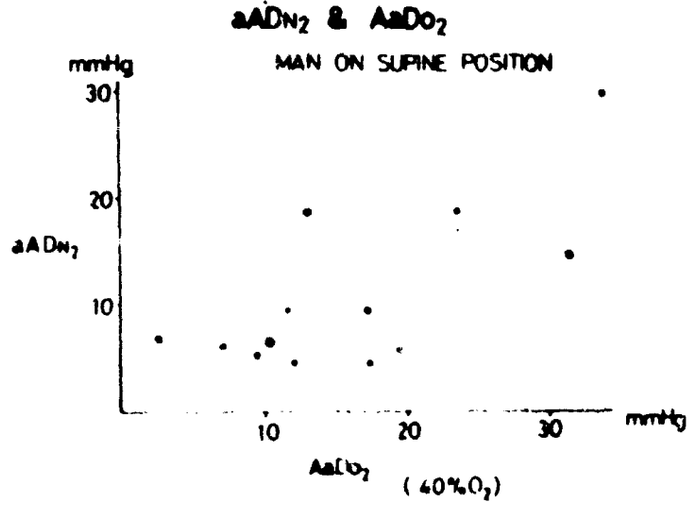

Fig.44. aADN2 vs.AaD02 on 40%02 level

7. EFFECT OF BRONCHODILATOR ON ARTERIAL-ALVEOLAR NITROGEN TENSION DIFFERENCE:

a. PURPOSE OF THE STUDY:

We have demonstrated the increased arterial-alveolar nitrogen tension difference in cases with some obstructive pulmonary diseases.

The present study was performed to find out whether or not the increased arterial-alveolar nitrogen tension difference in these obstructive pulmonary diseases would improve when the airway obstruction was improved by the administration of bronchodilator aerosols.

b. METHODS AND SUBJECTS:

aADN2 was measured on the patients accompanied by any obstructive ventilatory impairment. To examine the effect of bronchodilator upon uneven ventilation-perfusion distribution the subjects include patients with subacute or chronic bronchitis, chronic pulmonary emphysema and with the episodes of bronchial asthma.

The urinary specimen was collected anaerobically prior to the inhalation of the bronchodilator aerosol. The urinary nitrogen tension may represent the arterial nitrogen tension. The measurements were performed prior to and after the 5% isoproterenol aerosol inhalation.

Ten minutes after administration of bronchodilator aerosol the subjects again repeated the same procedure for the uADN2 measurements. Approximately 40 minutes after bronchodilator administration the second urinary specimen was collected. This interval was considered sufficient for equilibrating the urinary nitrogen tension with that in the body tissue under new steady state. The forced expiratory curve on the spirogram was again taken after the second urinary specimen was collected.

c. RESULTS:

The effects of the bronchodilator aerosols on uADN2 as well as on FEV1% are summarized in Fig.45.

The figure indicates FEV1% on the abscissa and the aADN2 on the ordinate. After the bronchodilator administration FEV1% did improved not in every cases. The aADN2 in every cases with obstructive expiratory incompetency revealed values exceeding normal limits. After bronchodilator inhalation these abnormally increased

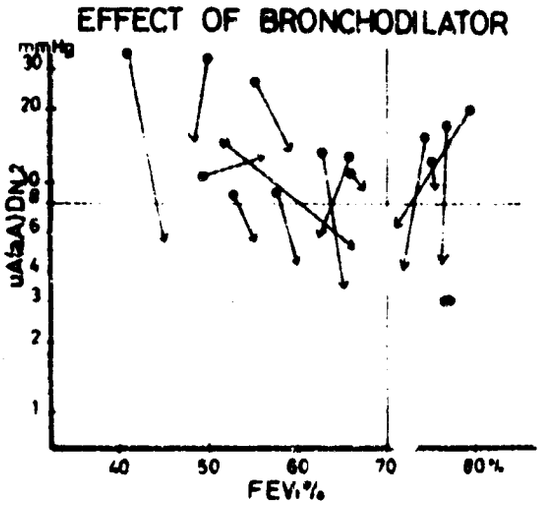

Fig.45. Effect of bronchodilator upon uADN2 as well as upon FEV1%.

aADN2 revealed any significant decrease. Even in cases, whose FEV1% was not improved after bronchodilator administration, this aADN2 was found improved. The relationship of changes in uADN2 as well as in FEV1% as indicated in the graph. The closed circles indicate the value prior to the bronchodilator inhalation and the open circles indicate those after the inhalation. The arrow connecting these closed- and open circles show the changes in these values.

8. EFFECTS OF CIGARETTE SMOKING UPON THE VENTILATORY CAPACITY AND THE ALVEOLAR GAS EXCHANGE:

a. PURPOSE:

The patients of Tokyo-Yokohama asthma were found among the population of heavy cigarette smokers. The cigarette smoking produce the" personal air pollution", which may be comparable to the"environmental air pollution" although the pollutant is quite different and although the effects upon the human body might be different. The epidemiological studies indicate high incidence of chronic bronchitis in the population of cigarette smokers than that of non-smokers.

In this chapter we will present some data obtained in the experimental observations on the effects of cigarette smoking upon pulmonary physiology. In this present series of experimental studies we aimed to make the following two points clear. One of them was the direct- and the immediate response of the human lungs to the cigarette smoking. Another was the long-term effects of cigarette smoking upon the pulmonary functions. Most of the clinico-physiological studies on the effects of cigarette smoking focused their aim upon assessing the obstructive ventilatory impairment produced by. The cigarette smoking may possibly produce as its proper pharmacological action the bronchoconstriction and it may also cause any further bronchoobstruction secondarily by producing excess mucous secretion. We assumed these bronchoobstruction may possibly cause uneven ventilation-perfusion ratio distribution.

b. METHODS AND SUBJECTS:

As for the subjects the volunteer healthy young doctors were taken. Some doctors had smoking habit of consuming more than 20 cigarettes daily and others were non-smokers.

Every subjects revealed neither physical findings nor chest X-ray abnormality.

These subjects were tested on the following program. The spirography with the respirometer of 13.5L Benedict-Roth type was first made. Measurements of the airway resistance using the body plethysmograph of pressure type was also done by the panting method. In parallel to these tests the urinary-alveolar nitrogen tension difference was measured. The urinary nitrogen tension was calculated from the data obtained by the gas chromatography. The detailed method for the analytical procedure has already been described.

Precisely constant volume of samples of approximately 0.2ml was used for analysis. Under the analytical condition the argon-free nitrogen peak on the gas chromatogram came out satisfactorily linear. For the calibration of the gas chromatogram the same urine or blood was equilibrated with the room air in the Farhi's tonometer at 37.3C to give the control peak height on the gas chromatogram. These peak height of gas chromatogram produced by the sample and the exactly same amount of this equilibrated specimen allowed us to calculate the argon-free nitrogen tension in the sample without using the assumed solubility coefficient for nitrogen. Triplicate analysis on each specimen was made to minimize the analytical error.

c.RESULTS FOR THE IMMEDIATE EFFECTS:

(1) SPIROGRAPHY:

The immediate effects of cigarette smoking on the ventilatory functions were studied. One hour pior to the tests subjects were requested not to smoke cigarettes. After the spirogram was taken the subjects smoked cigarettes for the tests and the ventilatory functions were again tested right after the smoking.

The Tables 23 and 24 indicate these summarized spirographic data on %VC, FEV1, FEV1%, MMF and on %MVV. Each of them are represented by the mathematical means. These mathematical means did not show any consistent changes, which was expected to occur immediately after the cigarette smoking. Although these values did not revealed any change in general, some spirographic data as compared with those obtained prior to smoking. As shown in the Table25 vital capacity, FEV1 and MVV appeared to decrease slightly right after

EFFECTS CIGARETTE SMOKING

	% V C %	$FEV_{1.0}$ % %
PRIOR TO SMOKING	114	84.9
RIGHT AFTER SMOKING	115	83.6

Table 23. Effects of cigarette smoking(1)

EFFECTS OF CIGARETTE SMOKING

	FEV_{10} L	MMF L/SEC	% MVV %
PRIOR TO SMOKING	4.13	4.63	135
RIGHT AFTER SMOKING	4.16	4.74	130

Table 24. Effects of cigarette smoking(2)

EFFECTS OF CIGARETTE SMOKING

	before smoking	right after smoking	30min.after smoking
VC (L)	4.93	4.79	4.88
FEV.% (%)	78	78	79
FEV (L/sec)	3.83	3.70	3.90
MVV (L/min)	171	151	171

SUBJECT : T.Y.

Taole 25. Effects of cigarette smoking on the ventilatory capacity. A case revealed sensitive response upon cigarette smoking.

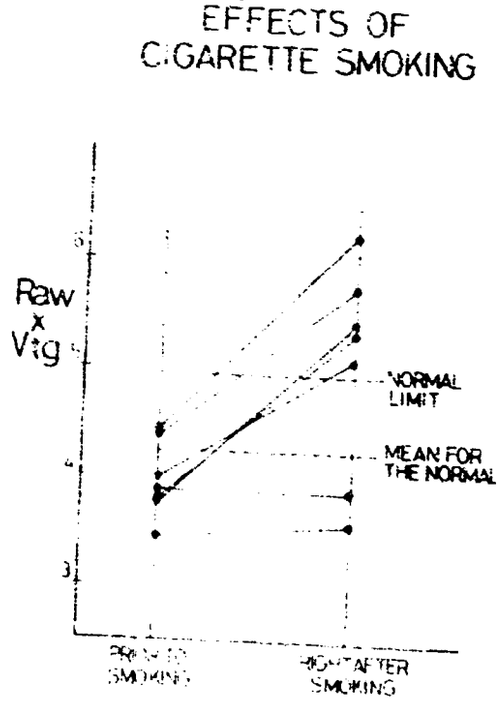

Fig.46. Effect of cigarette smoking upon airway resistance

smoking. In five repetitive spirography, excepting only one test, we found the same tendency to decrease in their ventilatory capacity. These data indicate the fact that some particular subjects could be highly sensitive in responding with their ventilatory functions to the cigarette smoking although in average they did not.

(2) AIRWAY RESISTANCE:

The immediate effects of cigarettes smoking were also studied by measuring the airway resistance using the body-plethysmograph. The RawXVtg was taken as the parameter to evaluate. This parameter was measured prior to and after cigaretd smoking. We have already set the mean for the RawXVtg on the normal subjects as 4.15cmH20sec and its 5% upper rejection limits as 4.96cmH20sec. As shown in the Fig.46 RawXVtg on seven healthy subjects prior to smoking remained within normal limits. After cigarettes smoking this parameter in five cases out of the referring seven subjects was increased over the 5% upper rejection limits while those in other two subjects the resistance remained unchanged.

d.CONCLUSION:

We have deduced the following comments:

1) The cigarettes smoking produce slight airway constriction, which may be detectable by the body-plethysmography.

2) This provoked airway obstruction was not significantly demonstrated on the spirography.

3) Some particular subjects demonstrated slight and temporary decrease in vital capacity,FEV1 as well as in MVV.

e.RESULTS OF THE LONG TERM CIGARETTE SMOKING:

The pulmonary functions on 283 volunteer subjects were examined with regard to their habit of cigarette smoking. This particular analysis was performed to examine the effects of long term cigarette smoking on the pulmonary physiology.

The subjects were divided into four groups, namely the"non-smokers","ex-smokers","smokers" and the heavy smokers". 34 cases were included in the group of "non-

smokers". 61 cases were included in the group of "ex-smokers", who had history of cigarette smoking although they had quitted smoking by the time of tests. 78 cases were "smokers", who used to consume less than 20 cigarettes daily. The fourth group was said to be the "heavy smokers", whose daily cigarette consumption was 20 cigarettes or more. Included in this group of "heavy smokers" were 110 cases. The age distribution in each four groups did not show any significant difference as shown in Table 26.

To minimize the immediate effects of cigarettes smoking subjects were requested not to smoke at least for 30 minutes prior to the tests.

The summarized spirographic data obtained on these four groups were given in the Tables 27,28,and 29. Tables indicate the mathematical mean and the standard deviation on %VC,FEV1%, and on MMF. As being shown in these tables the spirographic parameters for every four groups did not revealed any consistent difference. The spirography was not sensitive enough to pick up the effects of long-term cigarettes smoking.

The airway resistance measured by the panting method revealed any difference between "non-smokers" and "heavy smokers", as referred elsewhere.

9.CLINICAL OBSERVATION ON THE INCIDENCE OF AIRWAY IRRITATION:

a.PURPOSE OF THE STUDY:

By conducting some year-round clinical observations on the incidence of bronchitic patients on the specific population we tried to find out the general aspects of changing incidence of bronchitic patients. We also tried to find out the possibility of examining the patients, if he is really existed among Japanese population, accompanied by the similar symptoms with Tokyo-Yokohama asthma.

b.METHODS AND MATERIALS FOR THE OBSERVATION:

The observation was done mainly with regard to the clinical symptoms of cough,phlegm production and wheezing dyspnea as well as to the physical findings including chest X-ray abnormality.

The observations were performed on three different populations. One of them was the out-patients who visited the chest clinic in the Keio University Hospital. The second was the bank employee working in the Downtown of Tokyo. The third group was the group of employee of an

EFFECTS OF LONG-TERM
CIGARETTE SMOKING

MALE	NO.OF CASES	AGE MEAN	AGE RANGE
NON-SMOKERS	34	54.3	28 — 81
EX-SMOKERS	61	53.9	33 — 83
SMOKERS	78	50.5	24 — 73
HEAVY SMOKERS	110	52.0	30 — 78

Table 26. Subjects for the study

EFFECTS OF LONG-TERM
CIGARETTE SMOKING

% V C	MEAN	S D
NON SMOKERS	97.5 %	16.4 %
EX-SMOKERS	99.4	17.7
SMOKERS	101.9	17.3
HEAVY SMOKERS	91.4	15.4

Table 27. Effects of long-term cigarette smoking on %VC

EFFECTS OF LONG-TERM
CIGARETTE SMOKING

$FEV_{1.0}$ %	MEAN	S.D.
NON-SMOKERS	77.6 %	8.9 %
EX-SMOKERS	78.1	7.0
SMOKERS	77.9	6.8
HEAVY SMOKERS	77.5	7.1

Fig.28. Effects of long-term cigarette smoking upon FEV1.0%

EFFECTS OF LONG-TERM
CIGARETTE SMOKING

MMF	MEAN	S.D.
NON-SMOKERS	3.05 l/min	1.09 l/min
EX-SMOKERS	2.92	1.13
SMOKERS	3.00	1.21
HEAVY SMOKERS	2.85	1.04

Fig.29. Effects of long-term cigarette smoking upon MMF

Table 30. Incidence of bronchitis in a bank located in Downtown Tokyo.

month	no.of total patients	no.of patients with airway irritation	no.of patients with lower airway irritation
AUG,'66	38	8	2
SEPT	49	8	5
OCT	44	18	15
NOV	62	14	12
DEC	60	26	16
JAN '67	59	29	22
FEB	59	32	18
MAR	68	18	9
APR	48	10	4
MAY	48	8	6
JUN	38	8	2
JUL	42	11	2
AUG	48	10	3
SEPT	59	14	5
OCT8	72	16	10
NOV	64	34	8
DEC	78	32	22
JAN'68	54	24	18
FEB	48	22	17
MAR	52	18	12
APR	42	19	5
MAY	44	8	3
JUN	46	8	4

Figures in the table designate the mean numbers per day in the corresponding month.

semi-governmental firm located also in the Downtown Tokyo.

c,RESULTS OF THE OBSERVATION:

At the chest clinic of the Keio University Hospital we have calculated the numbers of outpatients on any particular date in summer and in winter seasons. The patients were classified into five groups, such as bronchitis,chronic pulmonary emphysema,bronchial asthma,pulmonary tuberculosis and others. The percentage of these classified patients is shown in Table 30. One can see the high incidence of bronchitis in winter season. This observation was done on the unlimited population and therefore it may be unable to give any definite conclusion.

We had an opportunity to continue some clinical observation on the incidence of bronchitis on the bank employee. The observation was performed in terms of the incidence of symptoms of the airway irritation on the limited population of approximately 2500 starting from August '66 thru June '68. During this period of observation the office building of the bank was moved to the new location in the Downtown Tokyo, where the air pollution was much worse than its original location. This allowed us to compare the data with regard to the effects of air pollution on the same limited population at different location. The observation was made basing upon the patients' subjective symptoms as well as their physical findings. To avoid the possible difference of the physician's individual impression the observation was done only by one chest physician, Dr.Yokoyama. He picked up the subjects out of all the patients visited at his office on a limited day of the week. The patients with airway irritation were divided into two groups with regard to their physical findings, namely the upper airway irritation with or without the lower airway irritation--the bronchitis. The patients with acute, subacute and chronic bronchitis were included in the latter group. Total numbers of the patients, numbers of patients complaining the symptoms of the airway irritation, such as sore throat, cough, nasal secretion,etc., were noted. The numbers of patients with airway irritation was divided into two groups as mentioned above. The patients demonstrated the evidence, such as nocturnal cough and sputum production as well as any physical findings of bronchial rale, were classified as the subjects of the lower airway irritation.

We could not expect much significance on the absolute

Table 31. Daily fluctuation of the incidence of bronchitis on the bank-population

date	no.of total patients	no.of patients with airway irritation	no.of patients with lower airway irritation
FEB.'68			
5	44	9	07
12	61	28	16
19	36	19	8
26	51	32	13
subtotal	192	88	44
mean	48	22	11
JUN.'68			
3	44	4	0
10	52	10	8
17	48	6	4
24	40	12	4
subtotal	184	32	16
mean	46	8	4

Figures in the table designate the ~~mean~~/numbers of corresponding patients on the particular date.

numbers of this bronchitic patients because in this present study we did not repeated the interview on the whole population concerned actively. But upon reviewing the data one can easily find the general tendency of the seasonal changes of the incidence of symptoms of airway irritation. It was low in summer and started to increase in September or October maintaining higher incidence through the winter seasons. The numbers of patients accompanied by the lower airway irritation, even during the winter seasons, revealed significant fluctuation. This fluctuation was directly related neither to the low environmental temperature nor to the temperature changes although the incidence of patients with the upper airway irritation was somehow related to the low environmental temperature.

We took the ratio of the numbers of patients with the lower-airway irritation to those with the upper and/or lower airway irritation. Although this ratio revealed significant day-by-day fluctuation it was consistently higher in average during the winter seasons than that during the summer seasons.

It seems difficult at this present stage of analysis to discuss this higher incidence in connection with the environmental air pollution. But as shown in Table 31 the incidence of bronchitic patients in December 67, January and February '68 appeared somewhat higher as compared with those in the winterseason of '66-'67. This might possibly related with the change of the location of the bank office to the more air-polluted area.

The patients were not always the cigarette smokers. The relationship between the incidence of airway irritation and the smoking habit was not quite significant. It may be interesting to compare the data in the winter season of '67 with that of '68 because the office building of the bank moved in into the more-air-polluted area in October'67. We have picked up at randomly each 12 days, namely three days from Nov.,Dec.,Jan., and Feb., in each winter seasons of '66-'67 and of '67-68. Every 12 samples were given the serial number at random so that each days picked up from two winter seasons made up 12 couples. The ratio of numbers of patients complained airway irritation and the total numbers of patients as well as the ratio of numbers of patients with the upper airway irritation vs.the upper and/or lower airway irritation were compared on each couples. The statistical analysis of these data indicated the consistent increase in the ratio in the winter season

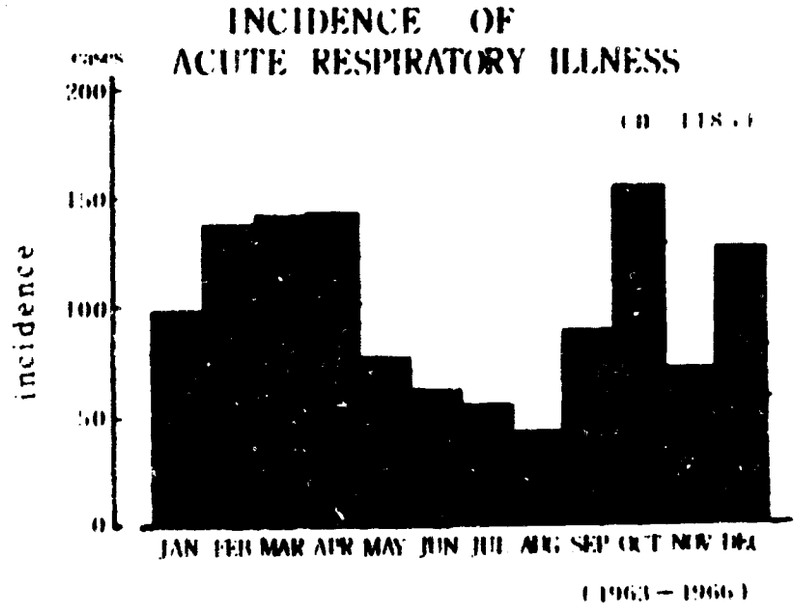

Fig.47. Incidence of bronchitis(acute) in a semi-governmental firm located in the Downtown Tokyo. Observation was continued from 1963 thru 1966.

of'670'68.as compared with that of '66-67. The ratio of the lower airway irritation to the upper and/or lower airway irritation was significantly higher in the winter season of'67-'68 than that in '66-'67.

The samples obtained on any windy days were compared with that on any cloudy,smoggy days. Each 15 days to meet these conditions were picked up at random and the overmentioned ratioes were compared on each couples. Thus we found on the cloudy days the numbers of patients with lower airway irritation was more profound than those on the windy days.

The background data concerning the cigarette smoking on this particular population was taken from the subjects picked up at randomly out of the particular population when they visited the clinic on any reason. These control subjects and the patients complaining symptoms of the airway irritation were divided into five groups with regard to their smoking habits,namely,A) the"heavy smokers" consuming 20 or more cigarettes daily,B) the"cigarette smokers" consuming less than 20 cigarettes daily,C) the "ex-smokers", who quitted cigarette smoking although he smoke cigarettes previously, andE) the"non-smokers".

Statistical analysis was performed on the incidence of airway irritation with regard to the habit of cigarette smoking. As shown in the table it was not able to dmmonstrate statistically any clear-cut relations between those two factors, namely the incidence of airway irritation and the habit of cigarette smoking.

The clinical observation was also done on the incidence of bronchitis at the other semi-governmental firm having the population of 1185. The accumulated data collected during 1963-1966 are shown in Fig.47. The accumulated number of bronchitic patients in each month is shown. The incidence of bronchitis is lowest in August and starts increase in September maintaining high incidence until April. This series of observation was conducted by Dr.Mitsufuji.

What was significant statistically in these series of observations was the higher incidence of bronchitic patients in every winter season. Significant daily fluctuations in the incidence as well as in the ratio were observed even during the winter season. This fluctuation was not related significantly to the

Table 32. Classification of patients in the chest clinic of the Keio University Hospital, Tokyo, Japan

Month observed	JAN'62	SEPT'62	JAN'63	MAR'63	AUG'66	OCT'66	MAR'67
No. of patients per day	111	98	68	74	59	87	58
BRONCHITIS	40	37	52	39	9	31	42
EMPHYSEMA	16	12	13	18	11	14	11
BR. ASTHMA	8	14	6	10	3	6	8
PULM. TBC	13	18	15	18	19	12	11
OTHERS	23	19	14	15	58	37	28
Total	100	100	100	100	100	100	100

Figures in the table indicate the percent incidence of the pulmonary diseases seen at the chest clinic, Keio University Hospital. The indicated date was picked up at random.

environmental air temperature. The ratio of lower airway irritation indicated something interesting in the clinical survey.

The quantitative analysis of air-pollutant was not done in this present study so that it is difficult to discuss it definitely at this present stage of the study in relation to the environmental air pollution. But it is quite suggestive that this higher incidence of bronchitis in winter seasons is related to the environmental air pollution.

10. THE FINAL COMMENT:

The proposed investigations on the effects of air pollution among Japanese civillian population were conducted mainly focusing upon the pulmonary physiology. What we have found will be summarized in the following comments:

a) METHODS FOR DETECTING THE OBSTRUCTIVE VENTILATORY IMPAIRMENT:

The spirography, which is routinely used for the epidemiological survey of the airborne bronchitis, is not sensitive enough to detect any minor changes. FEV1%, for example, has revealed some unavoidable error including any subjects' individual difference. Theefore we have given the 5% rejection limit for FEV1% in addition to its mathematical mean. If we take this 5% rejection limit for the diagnostic criteria the sensitivity of FEV1% for detecting minor airway obstruction might be spoiled.

The best measure to detect this minor changes in the airway would be the specific airway conductance measured by the body-plethysmographic method.

b) ARTERIAL ALVEOLAR NITROGEN TENSION DIFFERENCE TO DETECT THE IMAIRED VENTILATION-PERFUSION RELATIONSHIPS IN BRONCHITIC PATIENTS:

The impaired alveolar gas exchange probably due to airway obstruction in the bronchitics were demonstrated. The carbon monoxide pulmonary diffusing capacity may routinely be used to detect the impaired overall alveolar gas exchange.

We have shown the significance of this arterial(or urinary)-alveolar nitrogen tension difference and also have proposed the possible availability of this arterial alveolar nitrogen tension difference for the pulmonary function survey on the airborne pulmonary diseases. This parameter was found more sensitive than FEV1%.

The authors are to emphasize the physiological significance as well as the diagnostic importance of the proposed impairment of alveolar gas exchange seen in the bronchitic patients.

c) THE FLUCTUATING INCIDENCE OF AIRBRONE BRONCHITIS?

The year-round clinical observations on the limited population working in the Downtown Tokyo revealed high incidence of bronchitis in the winter season. These bronchitic patients did not complained any similar signs and symptoms with those found in patients accompanied by Tokyo-Yokohama asthma.

No evidence of showing any particular relationships with the cigarette smoking was found among these bronchitic patients.

STATISTICAL ANALYSIS OF THE MEAN
OF ANNUAL VENTILATORY CHANGES
PULMONARY DISEASE vs. NORMAL

	emphysema	fibrosis
V C	+	−
I C	+	−
ERV	+	−
MVV	−	−
FEV_1	−	−
$FEV_{1\%}$	−	+

+ ; significant at 5% level
− ; non-significant

Table 33. Comparison of the annual ventilatory changes of the chest patients with those of the normal healthy.

ANNUAL VENTILATORY CHANGES

Male ; Ht. 165 cm, Wt. 60 kg

	normal	emphysema	fibrosis
V C (L)	− 0.02	− 0.12	− 0.07
MVV (L/min.)	+ 1.7	− 2.5	− 2.2
FEV_1 (L/sec.)	− 0.05	− 0.07	− 0.03
$FEV_1\%$ (%)	− 1.0	− 0.5	+ 0.5

Table 34. Annual ventilatory changes represented as the standard Japanese subject.

Table 35. Ventilatory functions among 338 cases with chronic bronchitis

VENTILATORY FUNCTIONS	NO.OF CASES	% INCIDENCE
normal	102	31
restrictive impairment	41	12
combined impairment	106	31
obstructive impairment	89	26
total	338	100

Table 36. Incidence of bronchitis and cigarette smoking(1) APRIL-UNE,'67

	lower airway irritation	upper airway irritation	without irritation
heavy smokers	8	6	12
smokers	4	8	14
ex-smokers	2	5	9
non-smokers	12	19	23
total	26	38	58

Table 29. Incidence of bronchitis and cigarette smoking(2) SEPT.-DEC.'67

	lower airway irritation	upper airway irritation	without irritation
heavy smokers	12	9	6
smokers	7	4	8
ex-smokers	5	6	8
non-smokers	24	14	8
total	48	33	30

ACKNOWLEDGMENT:

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13. ABSTRACT

The pulmonary function studies included: a. the assesment of the spirometry and the mechanics of breathing repeatedly done on the limited population.

b. the bascline studies on the routine pulmonary function tests.

c. some fundamental observations of the airway resistance, the AaD and of CO pulmonary diffusing capacity on the cases of normal healthy as well as of chronic pulmonary diseases.

d. effects of bronchodilator and of cigarette smoking on the ventilatory capacity and on the alveolar gas exchange.

The year-round clinical observations were performed on the population with regard to the incidence of bronchitics and the correlation of this incidence with the cigarette smoking habit. (Author)

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